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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

APRIL, 1956

ORIGINAL ARTICLES

CLUES TO BETTER UNDERSTANDING OF THE NATURE AND TREATMENT OF CERTAIN INFECTIOUS DISEASES*†

By Theodore E. Woodward, M.D.
PROFESSOR OF MEDICINE

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In spite of notable advances in the clinical and antimicrobial management of important infectious diseases, namely, rickettsioses, meningitis, pneumonia, septicemia, endocarditis, cellulitis, plague, enteric disease and others, which have reduced drastically the incidence of death in pediatric and adult patients, mortality has not been erased nor have important residual tissue changes been totally reversed. Pathogens causing many of the important diseases may, on occasion, elude detection in the early stages of illness and, if proper specific therapy is withheld, may attack the tissues so rapidly as to outdistance treatment. Not infrequently a patient may die, "bacteriologically cured": a therapeutic paradox. Expressed in another sense, what is the underlying basis for toxemia? Patients are described as being "toxic," and yet information is lacking as to how a pathogenic agent alters the tissues or inalterably damages a cell beyond repair with resultant clinical toxemia and death.

There has been a reawakening of interest in the more fundamental nature of infections, now that the virtues and limitations of chemotherapeutic agents have been recognized. Except for certain notable exceptions such as infections caused by staphylococci, *Proteus vulgaris*, resistant streptococci, pyocyaneus and a few others, the therapy of many infectious processes presently amenable to control leaves little room for improvement. Death in meningitis, pneumonia, rickettsioses, plague, septicemia and other diseases usually is attributed to irreversible tissue changes that have transpired prior to the administration of the effective chemotherapeutic agent. It is now necessary to characterize fully the underlying biochemical and physiological disturbances that have been invoked by the offending microörganism or its toxin. Once the nature of these underlying alterations within the cell is known, supportive care on a more fundamental basis may be instituted. With little stretch of the imagination, one can envision the

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future treatment of serious infectious processes by: 1) administration of an antibiotic for microbial control and 2) the administration of an essential metabolic substance or substrate necessary for proper cell function. Only enlightened research in these fields will provide the clues to these mysteries. Dubos[3] is one of the current leaders who has rekindled interest in "biochemical determinants of infection."

Certain pertinent clinical, therapeutic and physiologic problems serve to illustrate these trends. Models chosen for discussion are the rickettsioses, epidemic hemorrhagic fever, meningococcal infection and important diseases of the Gram-negative group.

I. **Role of Capillaries and Small Blood Vessels in Pathogenesis of Disease.** Epidemic hemorrhagic fever, a serious illness, first attacked American soldiers in Korea during the spring of 1951. This illness, characterized by fever of 5 o 7 days' duration, headache, myalgia and a bleeding tendency with petechiae in the skin, mucous membranes and, in serious cases, the kidney, musculature of the right atrium, lungs, pituitary, adrenals and elsewhere, often led to death. Renal failure with shutdown, proteinuria and azotemia was a common accompanying feature.

During the course of the illness, which in the severely ill lasted 2 to 3 weeks, shock developed on about the fifth day. During the shock, hemodynamic studies revealed relative hypovolemia, and death could be delayed for a short time by copious administration of adrenergic drugs such as norepinephrine. Following abatement of the shock phase, however, the patient might develop a relative hypervolemia and die as a result of pulmonary hemorrhage, edema or bleeding into other vital organs. The etiologic nature of this illness has eluded detection. In spite of these disappointments, including the failure to develop a satisfactory specific chemotherapeutic agent, observations of the physiologic changes of blood vessels led to an important tributary of knowledge.

Greisman[5] noted that the capillaries of the nail bed in the shocked patient were dilated and that the motion of red blood cells (vasomotion) was sluggish. The reaction abated with normal vasomotor tone returning as convalescence began.

On inoculation of plasma from the shocked patient into anesthetized rabbits, vasodilatation with sluggish motion was noted in capillaries in about one minute and continued for approximately 10 minutes. The effects of this vasoreactor substance could be blocked in animals by the administration of cortisone, antihistaminic drugs (Benadryl) or plasma from convalescent patients.

Wisseman and Greisman[24] subsequently demonstrated that this type of vasoreaction was not specific for patients with epidemic hemorrhagic fever but occurred when plasma obtained from patients starved for 24 hours was inoculated into the experimental animal. Furthermore, these observers noted that the prior administration of glucose to the hemorrhagic fever patient or the fasted volunteer would negate the vascular response.

A vasoreactive fraction is present in the plasma of humans sufficiently potent to dilate the terminal capillary vessels of animals, provoke standstill of blood flow, produce tissue edema and ultimately cause death. The precise nature of this material has not been elucidated. The phenomenon may actually represent an ill-defined immunologic blood reaction which may fluctuate with the nutritional state of the host and hence may not represent the presence of a specific circulating vascular toxin. While the idea of a

specific circulating hematoxin remains a plausible one, the experience in epidemic hemorrhagic fever serves to emphasize the difficulties encountered in differentiating this hypothetical toxin from the complex vasoreactive substances of immunologic and endogenous origin[24].

tracer substances (Dextran and an azoprotein, T-1824-albumin), leakage of plasma was demonstrated with edema throughout most of the tissues including the muscle, pancreas, kidney, heart, and others, all indicating extensive increased permeability and capillary leakage. The extravasation of

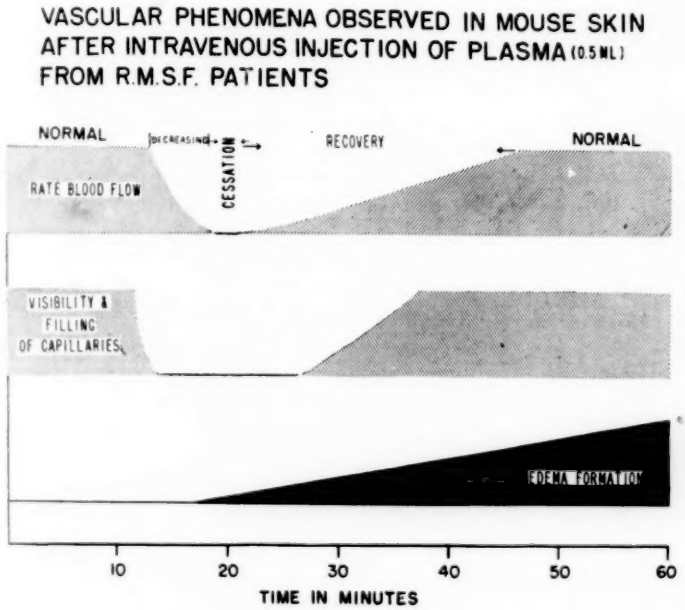

Fig. 1.—Vascular phenomena observed in mouse skin after intravenous injection of plasma from Rocky Mountain spotted fever patients. (Liu, R. S. J.[6].)

Wattenburg *et al.*[23] have succeeded in demonstrating potent vasoreaction by inoculating a rickettsial toxin into mice. Following intravenous inoculation of toxin, direct observation revealed that arterioles were greatly reduced in caliber, pre-capillaries disappeared from view, vasomotion accentuated and tissue edema resulted from leakage of plasma from the circulatory system.

These observers showed concurrent hemoconcentration (increased hematocrit) as a result of plasma loss. Utilizing plasma from the intravascular compartment into the tissues as a result of the rickettsial toxin is striking.

Although the mechanism is unknown, it would appear that rickettsiae or toxin exert their effect by direct action on endothelial cells[23]. During the spring and summer of 1954, Liu[6] demonstrated a similar vasoreactor effect in mouse capillaries following the inoculation of whole, untreated plasma from patients acutely ill with Rocky Mountain spotted fever. Increased vasomotion with venous dilatation, stasis

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and edema of subcutaneous tissues was demonstrated as shown by the following graph.

The problem as to how rickettsia or its toxin acts upon blood vessels is unknown but the mechanics seem clear. This vasomotion and capillary permeability provides a supplementary explanation for the early and late vascular manifestations in Rocky Mountain spotted fever.

It is a striking fact that antibiotic treatment, if given sufficiently early, will arrest these vascular defects, apparently by arresting rickettsial growth and subsequent toxic changes.

The toxic action by rickettsiae on capillary endothelium may involve alteration of essential metabolic pathways. Wisseman *et al.*[25] have demonstrated that suspensions of *Rickettsia mooseri* may oxidize glutamic acid through pathways involving alpha ketoglutamic, succinic, fumaric, malic, oxalacetic and pyruvic acids. Rickettsiae conceivably may compete with their host cell for these Krebs' cycle intermediates to such an extent that capillary damage might result from diminished production of high energy phosphate bonds. Greiff and Pinkerton[4] have shown that rickettsiae multiply rapidly in a medium of low oxygen tension, particularly in the tissues of fertile eggs when respiratory enzymes, such as the cytochromes, have been blocked by cyanide. On the other hand, a respiratory catalyst, such as methylene blue, which may by-pass the cytochromes, suppresses rickettsial growth.

Although patients now rarely die from clinical rickettsioses, the shortening of the course of disease in late cases remains a challenge. Undoubtedly, a clearer understanding of physiological abnormalities in the capillaries and elucidation of the intermediary metabolic aspects will provide the basis for even sounder supportive therapy.

II. **Persistence of Microörganisms in the Host and the Relapse Problem.** Various microörganisms reside in tissues of the human host without causing overt manifestations of illness. Examples include the rickettsiae in Brill's disease, typhoid bacilli and the typhoid carrier state, plasmodia of malaria and numerous viral agents of which herpes is a prime example.

Recently, *Rickettsia rickettsiae*, the causative agent of Rocky Mountain spotted fever, was isolated from the lymph tissues of a convalescent patient 14 months after subsidence of the acute infection[11]. This ability of viable rickettsiae to reside in the tissues of convalescent patients months after the active infection has been demonstrated in scrub typhus[17] and epidemic typhus[13]. Zinsser hypothesized that Brill's disease was recrudescent typhus fever caused by rickettsiae that had resided in the host for years after the initial illness. Thus, latent or inapparent infections may remain unnoticed, yet, for reasons not understood, this equilibrium may be upset and active disease develop.

It is of interest that the last 3 cases of Brill's disease (recrudescent typhus) which occurred in Baltimore demonstrated a dual factor implicating a stress phenomenon. Historically, each patient had typhus fever in Europe at least 10 years previously. Each developed fever, headache, rash and other classic features of recurrent disease while convalescing from a surgical procedure, namely, thyroidectomy[14], paronychia requiring incision[1], and cholecystectomy, respectively. Why should these latent rickettsiae suddenly escape their confines within the cell and again provoke disease? Similarly, quiescent malaria is frequently reawakened following surgical trauma or superimposed infection.

Price has succeeded in causing recurrent rickettsial infection through

stress mechanisms[13]. In primates experimentally infected with rickettsiae, second infection is provoked months later by administering large doses of corticoids. The recurrent disease cannot be ascribed to reduction of antibody by hormonal influence. Important clues are to be found here, since the nature of these phenomena is poorly understood. Dubos emphasizes that accumulation of lactic acid in tissues from inflammatory exudates exerts potent bacteriostatic and bactericidal action, in contrast to accumulated keto acids which favor infection[3]. Possibly similar factors of altered metabolic equilibrium account for the renewal of rickettsiae and other microbial infection.

Recrudescence of clinical infection soon after the subsidence of active disease poses a problem of more than academic interest. In patients with rickettsioses, typhoid fever, tularemia and brucellosis (intracellular parasites), specific therapy may arrest the manifestations of illness, yet if the timing is faulty, a relapse may ensue.

When patients with scrub typhus fever, ill for 5 days or more, are treated with suppressive antibiotics, acute manifestations usually abate within 24 hours and convalescence is uneventful, whether specific therapy is continued for a week or as briefly as one day.

However, when patients with the same rickettsial diseases are treated early in the course of infection before sufficient antigenic stimulation and immunity have ensued, relapse will occur and rickettsiae are readily reisolated from the blood.

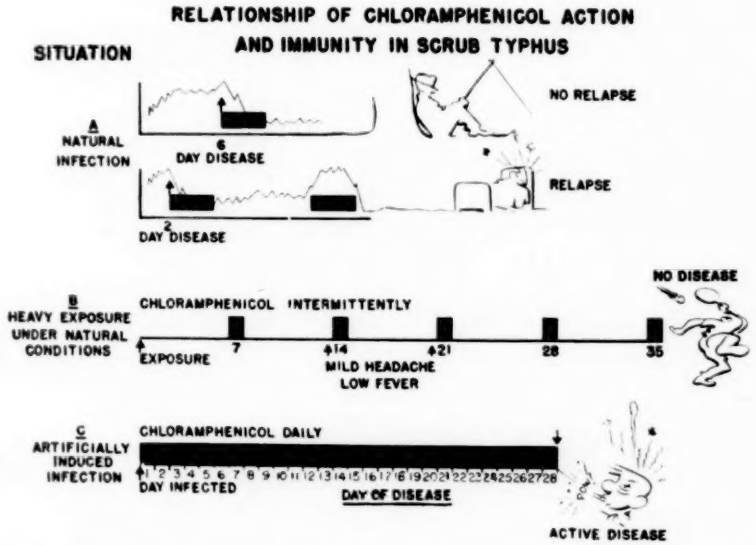

Fig. 2.—Relationship of chloramphenicol action and immunity in scrub typhus. (Reprinted from Dynamics of Virus and Rickettsial Infections, New York: Blakiston Co., 1954, p. 450.)

By proper spacing of antibiotic therapy through intermittent regimens, relapses may be prevented[15].

The relation of immunity and time of therapy in scrub typhus may be summarized as follows.

Under situation "A," relapses do not occur when specific treatment begins

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on or after the sixth day of disease, regardless of duration of treatment. However, when treatment is given quite early, such as the second febrile day, relapse ensues approximately 8 days after cessation of treatment. Situation "C" is a graphic presentation of the findings in a human trial in which rickettsiostasis by daily antibiotic treatment was maintained for 28 days after an artificially induced infection. Suppressive antibiosis for 28 days allowed insufficient time for immunity to develop under these conditions and full blown, active disease occurred in this group.

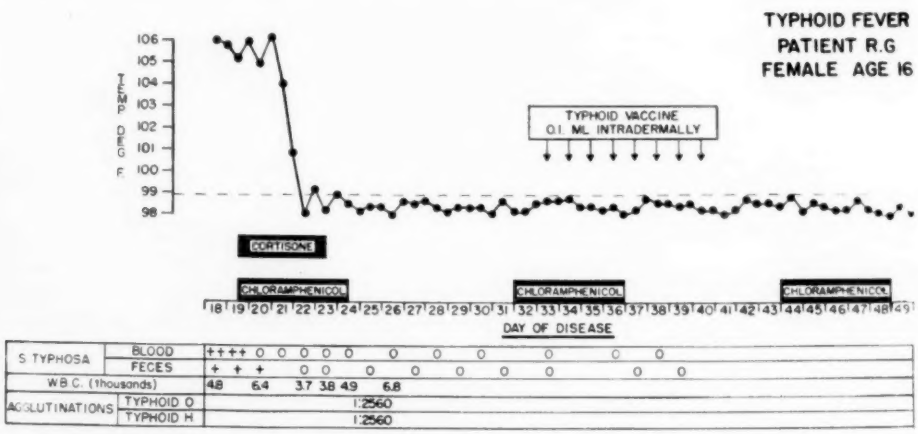

Fig. 3.—Regimen of intermittent chemotherapy and vaccine in patient with typhoid fever. Cortisone administered for acute toxemic properties.

In situation "B," it is noted that the intermittent administration of chloramphenicol at 7-day intervals in naturally infected human volunteers permitted the host to develop his own defense. Continuation of these intermittent courses up to the 35th day prevented the disease from appearing in the active sense. The mild headache and low grade fever noted just prior to several of the intermittent doses were undoubtedly manifestations of infection. At these times, *Rickettsia orientalis* was readily isolated from the patient's blood. Immunity, therefore, appears to be dependent in large part upon the mass of antigenic stimulation and resultant immune response.

Similarly, typhoidal relapses are noted more frequently in our current chemotherapeutic era. The 10% relapse rate formerly experienced by Osler now approaches 20% or more.

Relapse in typhoid fever usually occurs 15 days after the antibiotic is discontinued. Our concepts of drug administration in typhoid are similar to those in early rickettsial infection[27]; that is, intermittent application of the antibiotic with clinical suppression at crucial periods and rest periods allowing antigenic stimulation with bacterial multiplication with subclinical disease during the treatment interval. This regimen is demonstrated below.

An additional method of providing antigenic stimulation is the administration of killed typhoid vaccine as shown. Marmion, a British investigator, on the basis of a large series of cases studied, is convinced of the value of this combined regimen[7].

The ameliorating action of cortisone against the typhoidal toxin has been demonstrated under certain conditions in the experimental animal and its value as an antitoxemic agent in treatment of the human disease has been shown[16,26].

Thus, appropriate chemotherapy does not succeed in eradicating the microbe from the host; the same microbe may re-emerge from the confines of the cell at a later date and in the presence of waning or insufficient immunity again provoke disease. Immunity apparently comes at a price dependent upon the degree of antigenic stimulation and host reaction that has transpired by the time specific therapy is instituted. One does not interfere too greatly with the natural evolution of immunity if the timing is accurate.

III. **Nature of Underlying Lesion.** Certain microbial diseases are characterized by distinctive and occasionally explosive dermal reactions, namely, rickettsioses, meningococcal infections, septicemia and others. Although the histological features of the lesions have been described, the nature of the altered physiochemical environment leading to their development has not been clearly elucidated. Histologically, the vascular lesions of small and medium-sized blood vessels in periarteritis nodosa and the vascular nodule of rickettsioses bear some resemblance. In periarteritis nodosa, a disorder thought to arise as a result of hypersensitivity to various stimuli, there is endothelial swelling, cellular infiltration, fibrinoid changes and necrosis, with eventual thickening of the entire vessel.

Similar histological features characterize the lesion of Rocky Mountain spotted fever. The endothelial cell is swollen (rickettsiae multiply intracellularly in the intimal cells), the muscular layer is fragmented with necrosis and there is a florid proliferative reaction encircling the vessel. Platelet and leukocyte thrombi occur in periarteritis nodosa as well as in the rickettsial lesion.

Some investigators have been impressed with the similarity of the dermal lesions found in certain systemic microbial diseases and those in the experimentally produced Shwartzman reaction. The skin manifestations of meningococcemia fall into this category[18,21]. The Shwartzman reaction is brought about by inoculating a culture filtrate from certain Gram-negative bacteria intracutaneously. Local dermal inflammatory response at this site is produced by the intravenous injection of the same or other culture filtrates 24 hours later. Hemorrhage into the skin and necrosis do not develop until after the intravenous or provoking injection of toxin. The reaction in the prepared area has been attributed in part to leukocyte and platelet thrombi within small blood vessels[18].

The *generalized* Shwartzman reaction occurs when rabbits are given two successive intravenous injections of Gram-negative bacterial endotoxin, and consists of hemorrhagic necrotizing lesions in various organs, particularly the kidney (bilateral cortical necrosis)[19-21]. This reaction is apparently motivated by circulating polymorphonuclear leukocytes, since the reaction may be blocked by nitrogen mustard. Small blood vessels are occluded by eosinophilic material resembling fibrinoid. Platelet and leukocyte thrombi are likewise demonstrated. Thomas[20] employs this model to study the pathogenesis of the rheumatic lesion.

Recently, we observed a male youth on the second day of illness with all the clinical features of meningococcemia, that is, fever, headache, meningeal signs and purpuric rash.

Meningococci were isolated from a skin lesion. The meningitis and general manifestations of illness subsided rapid-

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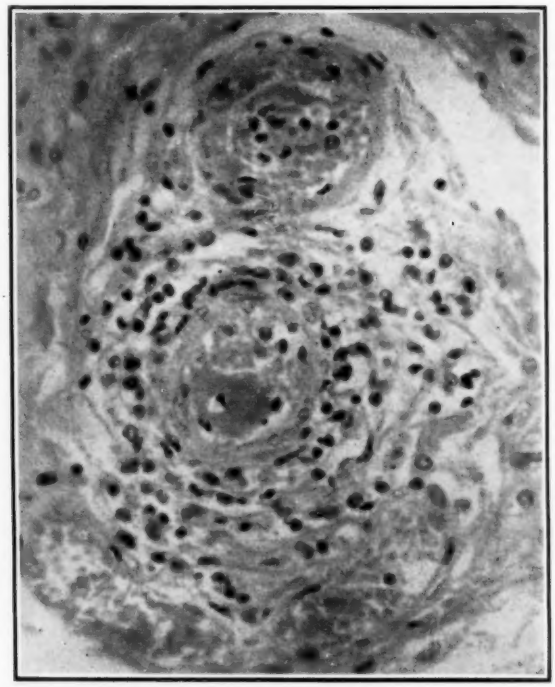

Fig. 4.—Rocky Mountain spotted fever. Vascular lesion in arteriole showing intravascular thrombi of leukocytes, endothelial swelling, and perivascular cellular proliferation.

Fig. 5.—Meningococcemia. Purpuric skin lesion prior to chemotherapy. Meningococci isolated from skin, blood and spinal fluid.

ly on appropriate chemotherapy. In spite of dramatic general improvement, however, mild low grade fever persisted and several skin lesions over the ankles and knees trebled in size, becoming hemorrhagic and necrotic and formed indolent, slow-healing ulcers. Culture of these lesions failed to reveal pathogenic bacteria.

Conceivably, these lesions developed as a result of a Shwartzman-like reaction following release of antigen coincident with chemotherapy, the latter patient described above did not receive cortisone.

The dermal hemorrhages of patients with Rocky Mountain spotted fever and epidemic typhus resemble those of meningococcemia. Developing more insidiously over several days, the lesions become purpuric, extensive and utimately slough to form indolent ulcers and, subsequently, scars.

Rickettsiae multiply in the capillary vessels of all organs including the skin. A rickettsial toxin probably is dispersed

Fig. 6.—Meningococcemia. Same lesion as shown in Fig. 4. Note extensive area of necrosis undergoing granulation and epithelization. Similar nonpyogenic, Shwartzman-like lesions occurred in other sites.

serving as a provoking stimulus to some of the already sensitized dermal areas. This type of reaction readily producible in rabbits with meningococci is rarely seen in human meningococcal infections. Why it occurred in this particular patient is unknown. In cortisone-treated rabbits inoculated intracutaneously or intravenously with bacterial toxin, extensive hemorrhagic lesions of the dermal and generalized type have been noted[19,22]. Similar clinical findings have not been reported in meningococcemia after cortisone therapy. The intravenously and, conceivably, the extensive vascular abnormalities which lead to necrosis may occur as a result of a Shwartzman-like phenomenon. One cannot disregard the direct action of rickettsiae upon the endothelial vessel, particularly in the capillary.

IV. **The Problem of Plague as Related to Time of Therapy and Toxemia.** Pneumonic plague, a disease of antiquity, elucidates why trends of management must differ from the conventional antimicrobial approach. Plague, caused by *Pasteurella pestis*, is mani-

fested frequently by a bubo which may subside uneventfully without too severe general reaction, although the over-all mortality in untreated bubonic plague is 30%.

Occasionally, the bacillus escapes the confines of the lymphatic system and produces a virulent and rapidly fatal septicemia. Patients with the septic type may develop a secondary pneumonia before death and spread plague bacilli via droplet routes. Pneumonic plague so produced is rapidly fatal, usually within 40 to 72 hours after the onset of illness.

Treatment of this highly fatal disease with broad spectrum antibiotics or streptomycin prior to the twentieth hour of illness uniformly results in recovery[8].

Of equal interest is the record of the following patient who succumbed to plague pneumonia. Specific treatment was not instituted until after the thirtieth hour of disease. In spite of prolongation of life for 36 additional hours, death occurred. The striking feature of the necropsy was the failure to demonstrate viable *P. pestis* in suitable bacteriologic preparations from the lung or liver: death with "bacteriologic cure."

This and similar situations emphasize the need for better understanding of the true nature of the underlying infection. The plague bacillus elaborates a potent toxin which exerts profound changes on blood vessels resulting in necrosis with small and extensive hemorrhages.

P. pestis produces a fibrinolysin which may contribute to the hemorrhagic tendency. The toxin possesses potent neurotropic properties. Reliable data relative to the metabolic defect provoked by the plague bacillus or its toxin are not presently available. Cortisone, of demonstrated value in ameliorating the toxemia in typhoid fever and

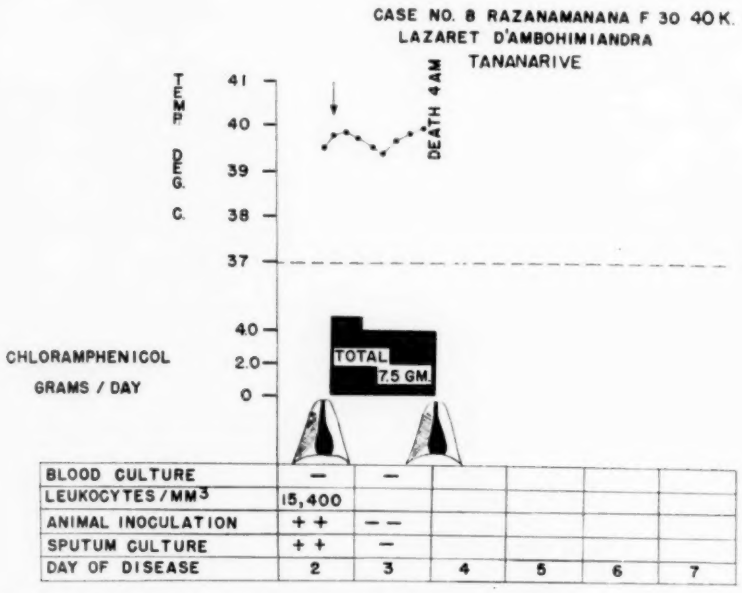

Fig. 7.—Pneumonic plague. Course of illness in fatal case first treated on second day of disease. (Reprinted from Am. J. Med., **14**, 289, 1953.)

scrub typhus, in limited trials has failed to alter significantly the course of plague patients late in their disease[8]. Hyperimmune serum has likewise been ineffective. Certainly, the gross lesions in the fatal case are not as extensive as physicians are accustomed to observe in many fatal illnesses. Conceivably, a metabolic defect remediable by appropriate biochemical replacement is a sound prophecy.

Fig. 8.—Human plague. Extreme vascular changes showing hemorrhage and necrosis in renal cortex of fatal case. Note interstitial extravasation of blood and tubular necrosis.

Problems related to understanding basic tissue alterations in infectious diseases are broad and complex, dependent upon a host of factors; for example, host reaction, character of the invading parasite and numerous intermediate considerations. The present discussion has neglected many vital contributions now under intense consideration by numerous investigative groups. The requirement for iron in metabolic substrates has been shown to be a variable and important factor in the production of diphtheria toxin, probably through interference with respiratory enzymes such as cytochrome B of *Corynebacterium diphtheriae*[9,10]. Techniques developed by Coons have led to better detection of the offending antigen in tissues during the early stages of infection[2]. By tagging anti-

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body with tracer of fluorescent stains and through utilization of proper photographic techniques, antigen may be detected within the host cell. Properdin[12], a recently characterized component of normal plasma, has been identified as a euglobulin possessing potent bactericidal properties.

These and many other noteworthy contributions in the immunological field will undoubtedly better clarify the nature of heretofore unexplained mysteries.

Conclusions and Summary. Many microbial diseases are now amenable to control as the result of drug action which denies the causative germ of an essential metabolite necessary for its growth. Sulfonamides rob the microbe of para-aminobenzoic acid, penicillin is thought to impede bacteria life by denial of glutamic acid and other essential substances.

So little is known of the metabolic alterations which pathogenic organisms effect in the tissues. Vital mysteries are concerned with the metabolic substrates which determine whether a microörganism may invade and cause disease, reside latently in a host cell, or die. Once invasive, what are the physiochemical alterations in the tissues which really account for the course of events?

Certain trends that investigation in infectious diseases must pursue are:

1. The vascular system, and particularly the capillaries, contributes to the pathologic-physiological tissue alterations in infectious diseases, that is, epidemic hemorrhagic fever, rickettsioses, meningococcal infections, plague, and others. To understand infectious disease processes, it is necessary to clarify the nature of increased capillary permeability.

2. Potent vasoreactor substances, capable of bringing circulation to a standstill in the capillary bed, are present in the plasma of patients with infectious disease and also in the normal individual under certain conditions. Much clarification is needed.

3. The toxins of rickettsiae, meningococci (in the broad sense) and plague bacilli possess potent vascular factors.

4. Microörganisms reside in the human host long after the initial infection. They may again provoke illness when the proper environment in the host is created. The nature of this environment is unknown.

5. Specific therapy administered for a short time to patients early in the course of scrub typhus may result in relapses. Relapses are common in typhoid fever and other diseases caused by Gram-negative bacteria. Interrupted or discontinuous therapy may prevent recrudescence. Combined vaccine-chemotherapy may have much in its favor, in certain instances.

6. Skin lesions of rickettsial disease and meningococcemia resemble the Shwartzman lesion.

7. The biochemist and physiologist, along with the microbiologist, immunologist and clinician, hold the key to the box of clues to the true nature of infectious disease.

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SUMMARIO IN INTERLINGUA

Multe morbos microbial es hodie dominabile, gratias al effecto de drogas que denega al germine causative un metabolito requirite in su crescentia. Sulfonamidos roba al microbio su acido para-aminobenzoic, e il pare que penicillina impedi le disveloppamento vital de bacterios per privar los de acido glutamic e altere substantias essential.

Nostre cognoscentias del alterationes metabolic effectuate per le organismos pathogene in le histos es ancora multo restringite. Mysterios vital se confronta con nos in le mechanismos del substratos metabolic que determina si un microorganismo pote invader le histos e causar un morbo, si illo es restringite a perdurar latentemente in un cellula hospite, o si illo debe morir. E si le histos es preste a esser invadite, qual alterationes physiochimic in le histos es vermente responsabile pro le subsequente curso del evenimentos?

Certe tendentias que debe characterisar nostre investigation del morbos infectiose es presentate in le sequente paragraphos.

1. Le systema vascular (e specialmente le capillares) contribue al histologic alterationes pathologico-physiologic de morbos infectiose, i.e., epidemic febre hemorrhagic, rickettsioses, infectiones meningococcal, plaga, etc. Ante que nos pote comprender le processos del morbos infectiose, nos debe clarificar le natura del augmentate permeabilitate capillar.

2. Potente substantias vasoreactive, capace a arrestar le circulation capillar, es presente in le plasma de patientes con morbos infectiose e sub certe conditiones

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THE PROBLEM OF SUBCLINICAL RHEUMATIC CARDITIS*

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The inflammatory lesion in the myocardium now known as the Aschoff body was first described by J. F. Goodhart in 1879. It remained for Aschoff[1] to establish a new era in the study of rheumatic fever when in 1904 he announced that this lesion is specific for the disease. Many attempts have been made in the past to correlate the clinical and pathological manifestations in fatal cases of the disease. However, it was not until very recently that the development of methods for the surgical correction of deformities of the mitral valve has made available cardiac tissue from living patients with rheumatic fever. The surgical approach to the diseased mitral valve involves the removal of a portion of the left auricular appendage and this has been submitted to extensive pathological investigation. By this method, a total of 1,180 auricular appendages have been evaluated up to this time (Table 1). In all those cases the preoperative diagnosis was mitral valvular disease of rheumatic origin and extensive clinical laboratory investigation had established the process to be inactive. Since the Aschoff body is generally regarded as the pathognomonic lesion of rheumatic disease, the majority of investigators have selected this lesion as the yardstick of clinical-pathological correlation. Available findings indicate that Aschoff bodies are found in the auricular appendage in about one-third of the cases of clinically quiescent rheumatic valvular disease[2-6,8-15,17,18] (Table 1). This has been interpreted as indicating that the rheumatic process can be active in the absence of clinical signs and symptoms.

Actually the Aschoff body is not a static structure and consideration to its life cycle is imperative in any attempt to correlate clinical and pathological manifestations. Discrepancies in the identification of the Aschoff body and in its significance can be expected to arise until it is generally understood that this structure passes through a life cycle[16,19].

Material and Observations. In the histological evaluation of 400 auricular appendages submitted to us for examination, we considered the rheumatic process to be active not in the presence of Aschoff bodies alone, but upon the identification of findings within the Aschoff body or in the myocardium or in the endocardium which could be interpreted as consistent with an early lesion. These findings included fragmentation of collagen fibers,

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alterations of the ground substance, degeneration of myofibers and exudative inflammatory reaction either in the Aschoff body, myocardium or endocardium (Table 2).

Following these criteria, 8 cases out of the 400 we examined (2%) were found to display unequivocal histological evidence of active rheumatic carditis. As in comparable series of other workers, extensive clinical-laboratory studies had established these 8 cases to be entirely inactive. The following are brief histories of the eight cases:

TABLE 1.—INCIDENCE OF ASCHOFF NODULES IN SURGICALLY REMOVED AURICULAR APPENDAGES

Author, Date	*No. of Cases*	*Incidence of Aschoff Bodies*
Pinninger[14] (1951)	15	10 (67%)
Waaler[18] (1952)	28	8 (28%)
Kuschner *et al.*[9] (1952)	11	4 (36%)
Sabiston and Follis[15] (1952)	43	32 (74%)
Biörck *et al.*[2] (1952)	18	8 (44%)
Janton *et al.*[8] (1952)	88	14 (16%)
Kuschner *et al.*[10] (1953)	28	14 (50%)
Enticknap[6] (1953)	71	29 (41%)
Decker *et al.*[3] (1953)	183	83 (45%)
Thomas *et al.*[17] (1953)	40	22 (55%)
McKeown[13] (1953)	53	24 (45%)
Denst *et al.*[4] (1954)	75	21 (28%)
Luse *et al.*[11] (1954)	77	32 (41.6%)
Elster *et al.*[5] (1954)	15	9 (60%)
Manchester *et al.*[12] (1955)	35	13 (37.1%)
Present series	400	75 (18.8%)
Totals	1,180	398 (33%)

TABLE 2.—CRITERIA EMPLOYED IN THE EVALUATION AND RESULTS

Healed or Healing Rheumatic Carditis

CRITERIA: (1) Aschoff body senescent in character*
(2) Endo-myocardial fibrosis
RESULTS: 392 cases, 98%

Active Rheumatic Carditis

CRITERIA: (1) Aschoff body, juvenile in character
(2) Alteration of collagen fibers and ground substance
(3) Exudative inflammatory reaction in the Aschoff body, myocardium or endocardium
(4) Degeneration of myofibers
RESULTS: 8 cases, 2%

* In 16.8% of cases

Case Reports. CASE 1. D.R., a 31-year-old white male was admitted to the hospital with a diagnosis of mitral stenosis. His temperature was 98.4° F.; pulse, 96; respirations, 21. His sedimentation rate was 4, leukocyte count 7,100 with a normal differential. Electrocardiogram showed right ventricular hypertrophy and strain. His blood pressure was 120/76. Roentgenographic study showed marked pleural reaction, right lung field; and cardiovascular changes consistent with mitral stenosis. Mitral commissurotomy was performed on July 16, 1953. Follow-up studies, after an uneventful postoperative course, reveal an excellent surgical result.

CASE 2. S.H.B., a 37-year-old white female, had her first attack of rheumatic fever at the age of 9. Preoperative diagnosis was aortic stenosis with insufficiency and mitral stenosis. The patient was on digitalis and was not in failure. Her temperature was 98° F.; pulse, 96; respirations, 22; sedimentation rate, 28;

and leukocyte count, 9,200. Roentgenographic study showed the heart enlarged, characteristic of mitral stenosis. Mitral commissurotomy was performed on June 29, 1953. The patient was not in good condition for further surgery. After operation, her temperature was 102° F., returning to normal on the fourth day after administration of penicillin and salicylates. Follow-up examination showed a blowing systolic murmur in the mitral area, first sound not sharp; mid-diastolic rumbling murmur with early diastolic murmur; Grade I to II rough systolic murmur in the aortic area; second aortic sound diminished followed by an early blowing diastolic murmur. Roentgenographic findings on January 16, 1954, were: heart enlarged to the right and pulmonary artery segment prominent. Digitalis was stopped and the patient appears to be doing well.

CASE 3. C.E.B., a 49-year-old white male, had his first attack of rheumatic fever at the age of 14. Preoperative diagnosis was mitral stenosis. His temperature was 98.6° F.; pulse rate, 60; respiratory rate, 18; sedimentation rate, 22; and leukocyte count 8,600, with a normal differential count. His blood pressure was 128/64. Roentgenogram showed cardiac changes compatible with mitral stenosis and pleural effusion at the left base. Mitral commissurotomy was performed on June 30, 1950. Postoperatively his temperature rose to 102° F.; pulse rate, 120; respiratory rate, 26; leukocyte count, 14,500 with 82% polymorphonuclears. There was evidence of a left hemothorax which eventually cleared. Since operation the patient has been checked at intervals and found to be asymptomatic.

CASE 4. D.S., a 30-year-old white male, had his first attack of rheumatic carditis at the age of 12. He has had recurrences of migratory polyarthritis every winter for the last 6 years. The preoperative diagnosis was mitral stenosis. His temperature was 98.2° F.; pulse rate, 70; respiratory rate, 20; blood pressure, 110/80; sedimentation rate, 10; and leukocyte count 7,300 with normal differential. Roentgenographic study showed cardiac changes consistent with mitral stenosis. Mitral commissurotomy was performed on July 14, 1953. His postoperative course was uneventful and follow-up has revealed no significant changes.

CASE 5. L.A., a 40-year-old white female, had been treated for congestive failure for 3 years prior to surgery. The patient was well compensated on digitalis. Electrocardiogram showed atrial fibrillation. The preoperative diagnosis was mitral stenosis. Her temperature was 99° F.; pulse rate, 60 to 80; respiratory rate, 20; sedimentation rate, 20; and leukocyte count, 9,400, with a normal differential. Roentgenographic study showed cardiac changes consistent with mitral stenosis. Mitral commissurotomy was performed on August 2, 1954. The postoperative course was uneventful and follow-up has revealed no change in cardiac contours although the patient is clinically much improved.

CASE 6. M.P., a 19-year-old white female, had been treated for acute pulmonary edema 6 months prior to surgery. She was well compensated on digitalis and routine therapy. The electrocardiogram was consistent with mitral stenosis of long duration. Her temperature was 99° F., blood pressure, 120/80; pulse, 70 to 90; respiratory rate, 20; sedimentation rate, 24; leukocyte count, 8,850, with a normal differential count. Roentgenographic study showed cardiac enlargement characteristic of mitral stenosis. Mitral commissurotomy was performed on October 18, 1954. After operation her temperature rose to 103° F. with return to normal on the fourth day. She was placed on cortisone immediately after operation. A follow-up examination on November 8, 1954, showed mitral murmurs present and the cardiac shadow unchanged. She was continued on cortisone for 6 more weeks. On January 4, 1955, examination showed a weight gain of 15 pounds, cardiac enlargement in the transverse diameter. Examination on April 12, 1955, showed the patient doing well and her weight stabilized.

CASE 7. MacV., a 30-year-old female, had her first attack of rheumatic carditis at the age of 7. Electrocardiogram showed ventricular hypertrophy, deformed P waves. Her blood pressure was 110/80; temperature, 98.4° F.; pulse rate, 86; respiratory rate, 20; sedimentation rate, 38; leukocyte count 7,800 with a normal differential count. Roentgenographic findings were consistent with mitral stenosis. Mitral commissurotomy was performed on September 20, 1954. After operation her temperature was 99° F.; pulse, 80; respiratory rate, 20; leukocyte count 17,000 with 86% polymorphonuclears; sedimentation rate, 46. She was discharged from the hospital on October 13, 1954, with a sedimentation rate of 34; leukocyte count 9,400. At follow-up examination the patient had developed signs and symptoms of dynamic aortic regurgitation. Clinically, the patient is doing well as of March 30, 1955.

CASE 8. E.I., a 28-year-old white female, was admitted to the hospital with evidence of advanced mitral stenosis, chronic heart failure and atrial fibrillation. Her tempera-

ture was 98.6° F.; pulse rate, 80 to 100; respiratory rate, 20; sedimentation rate, 7; leukocyte count 7,400 with 80% polymorphonuclears. Her blood pressure was 130/70. The roentgenographic findings and electrocardiogram were consistent with mitral stenosis. Mitral commissurotomy was performed on November 9, 1950. After operation her temperature rose to 101° F.; pulse 80 to 100; respiratory rate, 24; sedimentation rate, 14; leukocyte count 17,400 with 90% polymorphonuclears and a shift to the left. Her temperature returned to normal on the eighth day. Follow-up examination showed the liver and spleen not palpable and the cardiac shadow smaller than preoperative size.

Discussion. It is not the purpose of this paper to present the detailed clinical course of the above patients, but merely to indicate the type of case encountered in the presence of histological evidence of rheumatic carditis. The sedimentation rates are expressed in mm./hr. corrected for the Wintrobe method.

The auricular biopsies in all these cases showed Aschoff bodies juvenile in character, with large mono- or multinucleated cells having a vesicular nucleus and often a nucleolus. The connective tissue fibers were swollen, fragmented and granular in appearance. Fibrinoid alteration of the ground substance was demonstrated by special methods. There was an exudative inflammatory reaction within the Aschoff body and the adjacent myocardium and endocardium. In many instances the predominating cell in the inflammatory exudate was the eosinophilic leukocyte. All of the appendages in addition to the above changes showed evidence of endocardial and myocardial fibrosis. This association of recent and old lesions was thought to indicate an exacerbation of the rheumatic process.

Sixty-seven additional cases of our series (16.8%) displayed presence of Aschoff bodies in the absence of any evidence of acute tissue reaction. The chronic phase of the process was characterized by the appearance of senescent changes within the Aschoff bodies and by extensive myocardial and endocardial fibrosis. Most of the cells within the Aschoff body failed to reveal nucleoli so that they lacked the characteristic owl-eyed appearance. Instead, the nuclei were hyperchromatic and pyknotic often demonstrating karyolysis and karyorrhexis. Fibrinoid was not present and fibroblastic proliferation had taken place tending to obscure the outline of the Aschoff body.

In the remaining 324 auricular appendages (81.2%) no Aschoff bodies were found and the only detectable changes noted were endocardial and myocardial fibrosis. Since the Aschoff body has been regarded as the only pathognomonic lesion of rheumatic disease, the exact nature of the carditis and existing valvular deformity could not be established on strict morphological ground alone. In many of these cases the clinical history failed to indicate previous episodes of rheumatic fever. Consequently, the rheumatic origin of the mitral stenosis is based merely on the assumption that rheumatic fever is the most frequent offender of the mitral valve. Actually, the endocardial and myocardial fibrosis and the frequently associated valvular deformity are clinically more significant than the stigma of the process *per se*, the Aschoff body. The latter represents a reactive lesion, it appears relatively late in the course of the process (5th to 6th week[7]), and because of its small size and scattered distribution is not likely to interfere with the function of the organ. However, the extensive fibrosis may play a prominent role in the development of cardiac failure and represents the healed phase in the temporal sequence of events that take place in the primarily injured connective tissue.

Several investigators have questioned whether or not the findings in the auricular appendage compare with those in other parts of the heart. Twenty-two patients of our series died shortly after mitral commissurotomy. The microscopic findings of the heart at postmortem examination paralleled those of the surgically removed appendage, adding evidence in support of the contention that the auricular appendage is representative of the heart as a whole[8,17].

The medical record of the individual patients in each of the two pathological categories, active and inactive rheumatic carditis, was analyzed for any clinical-laboratory manifestation of activity. Clinical evaluation included detailed electrocardiographic and roentgenological procedures. Most patients were subjected to cardiac catheterization for pressure studies, estimation of blood volume and oxygen saturation. Preoperative blood samples were analyzed for complete blood count, hematocrit, sedimentation rate, urea nitrogen, C-reactive protein, antistreptolysin O titers and protein patterns (electrophoresis). The serological studies and sedimentation rate were repeated during the postoperative period. Comparative roentgenological measurements of heart size were also carried out preoperatively and postoperatively.

Except for elevation of the erythrocyte sedimentation rate, which in the majority of the cases correlated with the pathological classification, no other clinical or laboratory indication of preoperative activity was found in any of the 400 cases, including the 8 who had displayed unequivocable evidence of acute carditis in the biopsy specimen. The postoperative course also failed to reveal in any of the cases, signs, symptoms or laboratory data which might suggest recrudescence of the rheumatic process, and histologically active patients did not show any increase in operative mortality or morbidity as compared to the microscopically inactive cases.

Comment. The pathological changes observed in the 8 cases presented must be considered as reactivation of the rheumatic process. One would expect such tissue changes to evoke some sort of clinical picture. Except for an elevation of the sedimentation rate in 5 cases, the pre- and post-operative course showed a striking paucity of signs and symptoms commensurate with the acute tissue lesions. The possibility exists that the host response has been altered or modified. A more remote consideration would imply that the classical pathological concept of acute rheumatic carditis is in need of revision. The role of the antibiotics and steroid hormones on the course of rheumatic fever is not entirely understood. It is well known that cortisone will abolish the host response to an infectious process without affecting the infection. A discussion of the present-day concepts regarding the etiology of rheumatic fever is beyond the scope of this paper. However, it should be mentioned that if the Group A beta-hemolytic streptococcus initiates the rheumatic process, such organisms could persist in the host without signs of active infection while cortisone therapy was applied. Failure to correlate serological data with the tissue changes might reflect the enthusiastic use of antibiotics in eliminating the sensitive streptococcus before antibody formation can reach significant proportions.

Previous investigators have attempted to correlate the occurrence of mural thrombosis with the various stages of the rheumatic process[3,8,15]. Some believe that thrombosis develops more frequently in active carditis while others conclude that the incidence increases with the subsiding of the car-

ditis. No correlation could be found between thrombosis in the appendage and the stage of the rheumatic process determined microscopically in our series of 400 cases (Table 3).

TABLE 3.—INCIDENCE OF THROMBOSIS IN AURICULAR APPENDAGES

No. of appendages	400
Thrombosis present	66 (16.5%)
Thrombosis in healed or healing rheumatic carditis	65 (14.0%)
Thrombosis in active rheumatic carditis	1 (12.5%)

As indicated, the Aschoff body represents a highly characteristic lesion and it is justly recognized by the majority of workers in this field as the stigma of the rheumatic state. Since it was not found in all cases and varieties of factors may be operating in the evolution of the rheumatic state, the attempt to individualize the responsible factor or factors in this group of cases might result in the identification of the agent that elicited the Aschoff body itself. It might well turn out to be that the direct streptococcal injury may be the cause of the Aschoff body as a specific response of the host. Likewise fibrinoid alteration of the ground substance is found in some rheumatic hearts and not in others. Since the manifestations of the rheumatic state are not static, presence or absence of fibrinoid might be related to a phase in the evolution of the lesion. It conceivably might reflect a particular type of metabolic disorder brought about by a specific provoking agent. It has been suggested that the clinical manifestations of the rheumatic state have undergone a vast change in character. Since this condition is characterized by manifold signs and symptoms and lacks uniform clinical manifestations, this becomes exceedingly difficult to prove.

Summary. A total of 400 consecutive left auricular appendage biopsies removed during surgery for mitral commissurotomy have been reviewed. The assumption is made that the Aschoff body *per se* does not express rheumatic activity. The process was considered to be active in the presence of alteration of the ground substance, collagen fiber degeneration, regressive changes in muscle fibers and an exudative inflammatory reaction within or around the Aschoff body. Using these histological criteria in keeping with the changing phases of the rheumatic process, 8 cases of unequivocal active carditis were observed. Pre- and post-operative studies failed to substantiate the presence of tissue activity by clinical means. There was a striking lack of correlation between the tissue changes and blood studies including serological procedures. It is suggested that the discrepancies observed may be due to modification of the host response by the use of potent therapeutic agents.

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SUMMARIO IN INTERLINGUA

Le Problema de Subclinic Carditis Rheumatic

Esseva revidite un total de 400 consecutive biopsias del appendice sinistro-auricular, obtenite durante operationes pro commissurotomia mitral. Nos postula que le corpore de Aschoff per se non representa un expression de activitate rheumatic. Nos considerava le processo como active quando il habeva un alteration del substantia fundamental, un degeneration de fibras collagene, alterationes regressive in le fibras muscular, e un exsudative reaction inflammatori intra o circa le corpore de Aschoff. Iste criterios histologic esseva usate, de accordo con le varie phases del processo rheumatic, in le observation de 8 casos de inequivoc carditis active. In studios pre- e post-operative, medios clinic non revelava le presentia de histo-activitate. Il habeva un frappante absentia de correlation inter le alterationes histologic e le observationes hematologic, includente procedimentos serologic. Nos opina que le observate discrepantias es possibilemente explicabile como effecto del uso de potente agentes therapeutic.

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etiam in le plasma de individuos normal. Multe clarification es requirite in iste area.

3. Le toxinas de rickettsias, meningococcos (in un large senso), e bacillos de plaga possede potente factores vascular.

4. Micro-organismos reside in le hospite human a longe intervallos post le infection initial. Illos pote de novo provocar un stato morbose si le correspondente ambiente es create in le hospite. Le natura de iste ambiente non es cognoscite.

5. Specific therapias administrate durante breve periodos in le phases initial de febre fluvial japonese pote resultar in recidivas del patientes. Recidivas es frequente in febre typhoide e altere morbos causate per bacterios Gram-negative. Interruption o discontinuation del therapia pote prevenir recrudescentia. In certe casos un combinate therapia vaccino-chimic es possibilemente multo recommendabile.

6. Lesiones cutanee de morbo rickettsial e meningococcemia es simile a lesiones de Shwartzman.

7. Le biochimico e le physiologo, insimul con le microbiologo, le immunologo, e le clinico, manipula le clave al ver natura del morbos infectiose.

TREATMENT OF URINARY TRACT INFECTION WITH TRIPLE SULFONAMIDES AND A PENICILLIN-TRIPLE SULFONAMIDE MIXTURE. A COMPARATIVE STUDY

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Bacterial invasion of the urinary tract is nearly as common as infection of the upper respiratory system and may have more serious consequences[9]. With increase in the proportion of aged persons in the population, the incidence of urinary infections is likely to become even greater[13]. Cystitis, acute[4] or chronic, may occasionally be the expression of a localized inflammation, but usually is secondary to involvement of some other part of the urinary tract.

Of the relatively few organisms that invade the urinary organs, *Escherichia coli* is the major offender; others of the Gram-negative group, as *Aerobacter aerogenes*, *Proteus vulgaris* and *Pseudomonas aeruginosa*, occur less frequently. Of the Gram-positive organisms, *Streptococcus fecalis* and the staphylococcus are most commonly responsible for symptoms[8]. The Gram-negative species usually reach the upper urinary tract through the lymphatic vessels or by ascent from the bladder, generally as a result of external contamination; Gram-positive infections may be conveyed to the renal parenchyma or pelvis by the blood stream[13]. Whatever the route of the infection, eradication of the invaders from the tissues is the goal of therapy[9]. Blood and tissue concentrations of the therapeutic agent rather than urine levels, therefore, appear of greater importance, since the infection resides in the substance, not the lumens of the urinary channels[8].

Ideally, selection of the therapeutic agent should be based on preliminary identification of the infecting organism. However, from the standpoint of laboratory availability and time limitations, it is not always possible or practicable to carry out such procedures. Since the great majority of urinary infections are caused by sulfonamide-susceptible bacteria, treatment, especially of simple acute cystitis, is usually initiated with the sulfonamides[5,13].

Multiple sulfonamide preparations have introduced a greater margin of safety into chemotherapy, with lessened renal complications, especially crystalluria[2,10,11]. A triple mixture combining sulfadiazine and its dimethyl and monomethyl derivatives (sulfamethazine and sulfamerazine)[3,6,7,12,16-19] is reported[2,11] to provide high blood levels and excellent tissue diffusion, with some evidence of synergistic action[1,2,11]; and to afford more reliable protection of the kidney, with fewer evidences of sensitization[11]. Administered in a vehicle of aluminum hydroxide gel, the triple sulfonamide mixture is described as having produced higher initial blood concentrations of more prolonged duration than similar preparations containing no adjuvant[2].

Since in many urinary infections both

cocci and bacilli may be involved, it is also often desirable to employ a broader therapeutic approach. For such cases, a combination of sulfonamides and penicillin has been recommended[14].

The purpose of this study was to compare the effectiveness of two oral antibacterial agents, a sulfonamide preparation* and a sulfonamide-penicillin combination* for routine treatment of urinary tract infections in outpatient practice.

Selection of Patients. The series included 148 patients, of whom 98% were adult females. All presented symptoms and signs of acute or chronic bacterial cystitis, with or without clinical evidence of possible infection in the upper urinary tract. Many patients had gross or microscopic hematuria. In these cases, after cystoscopy and retrograde ureteropyelograms had ruled out other disease, a diagnosis of acute hemorrhagic cystitis was established.

In practically all cases there was no obstruction of the ureters or vesical neck, and no calculous or other disease of the urinary organs. Thus it was possible to conduct a well controlled study of both the bacteriology and symptomatology of urinary infection uncomplicated by diverticula, the presence of residual urine, or generally poor emptying function. The typical patient was an adult female complaining of a variety of urinary symptoms, occurring singly or in combination, and including frequency, dysuria, nocturia, incontinence, suprapubic distress, urethral pain, and introital burning or itching.

Method of Study. Initially, each patient was catheterized and the uncentrifuged urine specimen subjected to microscopic examination. A part of this sample was sent, under aseptic conditions, to the bacteriological laboratory for culture. Bacterial sensitivity studies were not done routinely.

The patient was then started on oral medication. Seventy-one in the series received the triple sulfonamides and 77 were treated with the triple sulfonamide-benzathine penicillin mixture. The course was started with an initial dose of 4 teaspoonfuls (20 ml., or 2 gm.), followed by 1 teaspoonful (5 ml., or 0.5 gm.), 4 times a day, contrasting the usually recommended dosage for sulfonamides, which is 2 to 3 times this amount. (Bayne and coworkers[1] have reported that 2 gm. triple sulfonamides initially, followed by 0.5 gm., 4 times a day, in a series of normal individuals, produced mean sulfonamide plasma levels that were adequate according to accepted standards[15]). Medication was taken after each meal and at bedtime, and was continued for a total of 7 days.

No local treatment to urethra or bladder was used since this would have distorted the picture.

All patients were advised to maintain a fluid intake of 2000 to 2500 ml. between arising and bedtime each day. Alkalis were considered unnecessary and were not prescribed. In certain cases anticholinergic drugs were administered for control of dysuria and bladder spasm.

Seven days after the treatment course was completed, each patient returned for a follow-up visit. At this time, details concerning clinical response to medication were recorded and a routine urological examination was done. A urine specimen was obtained by catheterization, under aseptic conditions, for post-treatment microscopic examination and culture.

Results. Symptomatic relief, usually complete, was obtained by practically the entire group.

The findings in the bacteriological studies (Tables 1, 2 and 3) are, for the most part, self-explanatory. Of the total 148 patients, 65% were infected by *E. coli*.

There appeared to be no significant difference in the effectiveness of the two preparations used in this study (Table 1). Of the group treated with triple sulfonamides alone, 79% were freed of urinary infection; in 21% the infection resisted treatment. Seventy-five per cent were treated successfully with the sulfonamide-penicillin mixture; in 25% infection persisted.

SIDE EFFECTS. Of the 148 patients studied, only 3 (2%) experienced side

*Sulfose Suspension (Triple Sulfonamides, containing sulfadiazine, sulfamerazine and sulfamethazine, 0.167 gm. of each, or a total of 0.5 gm., per 5 ml., in an alumina gel base); and Bicillin-Sulfas Suspension (containing 150,000 units, or about 150 mg., benzathine penicillin G, and 0.167 gm. each of sulfadiazine, sulfamerazine and sulfamethazine, per 5 ml., in an alumina gel base) were supplied by Wyeth Laboratories.

reactions to the drugs used. One who received the triple sulfonamides had headache and chills; of 2 treated with the sulfonamide-penicillin combination, one had a typical generalized skin rash and one had swelling and redness of the tongue. In all, symptoms of drug sensitivity subsided promptly on withdrawal of antibacterial medication and use of supportive measures (cortisone and antihistamines). Despite omission of alkalis from therapeutic regimen, there was no evidence of crystalluria, effective. The triple sulfonamide preparation was very satisfactory in the small group suffering from *Proteus vulgaris* infection; the organism was eradicated in 6 of the 7 cases.

In several of the urine cultures done 7 days after termination of the course, a number of organisms were demonstrated that had not appeared in the pretreatment studies (Tables 2 and 3). These bacteria, which probably had been repressed by overgrowth of the initial infection, perhaps were present

TABLE 1.—SECONDARY GROWTH PRESENT AT FINAL CULTURE

Triple Sulfonamides				*Benzathine Penicillin-Triple Sulfonamides*			
Organism	*No. of Cases*	*Good Results*	*Failures*	*Organism*	*No. of Cases*	*Good Results*	*Failures*
E. coli	42	32	10	*E. coli*	54	41	13
Hemolytic *Staph. albus*	2	2	0	Hemolytic *Staph. albus*	4	4	0
Staph. albus	5	5	0	Lactobacilli	2	2	0
A. aerogenes	7	5	2	*A. aerogenes*	4	2	2
Proteus vulgaris	7	6	1	*Proteus vulgaris*	2	1	1
B. alkaligenes	1	1	0	Hemolytic enterococci	1	1	0
Nonhemolytic streptococcus	2	1	1	Beta hemolytic streptococci	3	2	1
Pseudomonas sp.	2	2	0	Diphtheroids	3	3	0
Anaerobic streptococcus	1	1	0	Nonhemolytic *Staph. aureus*	1	1	0
Paracolon bacilli	1	1	0	Nonhem. enterococcus	2	0	2
Enterococci	1	0	1	*Strep. viridans*	1	1	0
	71	56 (79%)	15 (21%)		77	58 (75%)	19 (25%)

and no gastrointestinal disturbances, or other serious side effects, were observed.

Discussion. The result of treatment was considered "good" if the posttreatment urine specimen was negative for the original infection. The result was classified as "failure" if the urine continued to show presence of the organism initially demonstrated. In such cases bacterial sensitivity studies usually were performed to guide the selection of other therapeutic agents.

The coccal infections responded well to both agents, as expected. Against *E. coli* both drugs were about equally in a latent stage during therapy, and, therefore, were not affected by the medication; or the organisms may have occurred as secondary invaders or as culture contaminants. In any event, since most of the patients with secondary bacterial growth in the urine were symptomatically well, and posttreatment urine specimens were negative on microscopic examination, the presence of such organisms has no serious clinical significance. Perhaps, in a longer follow-up period, there might have been some recurrences. However, since no patient returned for additional treatment, it is believed that there were no

relapses in those freed of the initial urinary infection by the medication.

Postmedication cultures for the group treated with the penicillin-sulfonamide combination showed fewer secondary organisms (Table 3) than did cultures for the group who received the triple sulfonamides alone (Table 2). This is considered an indication that addition of penicillin to the triple sulfonamide mixture definitely increased the activity of the combination in suppressing secondary bacterial growth in the urinary tract.

Summary. A clinical and bacteriological study was conducted in 148 outpatients, of whom 98% were adult females, to compare the effectiveness of two oral preparations, a triple sulfonamide mixture and a combination of triple sulfonamides with benzathine penicillin, for uncomplicated acute and chronic infections of the urinary tract. Before start of medication, urine speci-

TABLE 2.—SULFOSE TREATED CASES; SECONDARY GROWTH PRESENT AT FINAL CULTURE

Initial Culture	*Secondary Growth*
Pseudomonas sp.	Paracolon
Paracolon bacilli	Alpha streptococci
E. coli	*Lactobacillus sp.*
	Hemolytic enterococcus
	Staph. albus
	Nonhemolytic enterococcus
	Hemolytic streptococci
	Nonhemolytic staphylococci (3 cases)
	Enterococcus and *Staph. albus*
	Nonhemolytic streptococci
	Diphtheroids
	Enterococcus sp.
	Hemolytic *Staph. albus*
	Proteus and Gram-positive cocci
	Staph. aureus
A. aerogenes	*B. subtilis*
	E. coli
	Nonhemolytic streptococci and hemolytic *Staph. albus*
Anaerobic streptococci	Diphtheroids
Nonhemolytic *Staph. albus*	Diphtheroids
	Enterococcus sp.
	Staph. aureus
Nonhemolytic streptococci	Nonhemolytic *Staph. albus*
Proteus sp.	Nonhemolytic *Staph. albus*
Hemolytic *Staph. albus*	Gram-positive bacilli
B. alkaligenes	*Staph. aureus*

TABLE 3.—SECONDARY GROWTH PRESENT AT FINAL CULTURE; BENZATHINE PENICILLIN-TRIPLE SULFONAMIDE TREATED CASES

Initial Culture	*Secondary Growth*
E. coli	Nonhemolytic streptococcus and enterococcus
	Nonhemolytic *Staph. albus* (4 cases)
	B. subtilus
	Hemolytic enterococcus
	Nonhemolytic enterococcus (2 cases)
	Gram-positive cocci
A. aerogenes	Staphylococcus
	E. coli
Nonhemolytic *Staph. albus*	Nonhemolytic enterococcus
Diphtheroids	Nonhemolytic enterococcus
Beta hemolytic streptococci	Hemolytic *Staph. albus*

mens were obtained by catheterization, and subjected to microscopic examination and culture. A variety of organisms were demonstrated, with *E. coli* present in 65%.

Medication was administered in an initial dose of 2 gm. followed by 0.5 gm. 4 times a day for 7 days (the dosage customarily prescribed for sulfonamides is twice this amount or more). Seven days after termination of the course, all patients received a routine urological examination, with laboratory study of the urine.

There was no significant difference in the effectiveness of the two drugs used. Of 71 patients treated with the triple sulfonamides, 79% were freed of urinary infection; in 21% the infective organisms resisted treatment. Of the 77 who received the penicillin-sulfonamide combination, 75% were treated successfully; in 25% infection persisted.

Both preparations were active against the coccal infections. The triple sulfonamide agent eradicated *Proteus vulgaris* in 6 of 7 cases.

The penicillin-sulfonamide combination was more effective than the triple sulfonamides alone in preventing secondary growth of organisms not present in pretreatment cultures.

Sensitivity reactions (headache, chills, rash, swelling and redness of the tongue) occurred in 2% but subsided promptly on withdrawal of antibacterial medication and use of supportive measures. There was no evidence of crystalluria, and no gastrointestinal disturbance or other serious side effect.

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(Interlingua on page 479)

INDUCED AZOTEMIA IN HUMANS FOLLOWING MASSIVE PROTEIN AND BLOOD INGESTION AND THE MECHANISM OF AZOTEMIA IN GASTROINTESTINAL HEMORRHAGE

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The cause for the elevation of the blood urea nitrogen concentration following massive gastrointestinal bleeding is controversial. Conflicting results have been reported by several observers. Schiff and his co-workers[6] showed that the azotemia was dependent upon the absorption of nitrogenous products from the blood in the gastrointestinal tract and was proportional to the amount present. Johnson[4], on the other hand, emphasized the role of the kidney and concluded that the azotemia following gastric hemorrhage did not occur in patients in the absence of reduction in renal function. Yuile and Hawkins[8], working with mongrel dogs, confirmed Schiff's observations. Black[1], in his critical review, concluded that the evidence suggested that the azotemia was due to the absorption of nitrogenous products derived from the blood in the intestine, when the kidney function was impaired by a diminished renal blood flow. Greenblatt and Cohn[2], presented data that supported the latter concept. They postulated that there was a critical level for blood loss in normal subjects which reduced the circulating blood volume causing impaired renal function resulting in azotemia. They demonstrated that there was no appreciable nitrogen retention or change in urea clearance following venesection and autoingestion of 580 ml. of blood; whereas, with 800 ml. a significant azotemia developed and a marked fall in urea clearance occurred.

In view of the conflicting reports, the present investigation was undertaken in order to study the effects, in normal subjects, of ingested protein of various types (beefsteak, protein concentrate and human blood), on the blood urea nitrogen and the 24-hour total urinary nitrogen excretion.

Methods. Five healthy male physicians, between the ages of 25 and 39 years, volunteered for this experiment. There were no histories of previous hypertension or renal disease and all had normal physical exami-

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nations. Three to 5 days prior to the experiment, urea clearance studies were performed. A routine urinalysis, including specific gravity and microscopic examination was done at the same time. The results of these tests were all normal.

Citrated human blood was obtained from the blood bank. This blood had been diluted in a ratio of 4 to 1 with a 4% solution of sodium citrate, so that 1,000 ml. of bank blood contained 800 ml. of whole blood. The average total protein content of the blood was 7.5 gm. per 100 ml. and the average hemoglobin was 15 gm. per cent. Thus, 800 ml. of whole blood was calculated to contain 180 gm. of protein. After a 10-hour fast, a Levine tube was passed into the stomach of 3 subjects, (A, B and C) and 1,000 ml. of the blood was administered to each in 15 minutes. The effect of psychic trauma appeared to be nonexistent. All maintained their usual daily activities. They were permitted to drink up to 2,000 ml. of water and to smoke. Except for an occasional piece of peppermint candy, no other food was eaten for 24 hours. Blood was drawn from each for urea nitrogen determinations, prior to the blood ingestion and at 2 to 3-hour intervals for 11 to 14 hours and 24 hours later. Twenty-four hour urine specimens were collected under toluene and analyzed for total nitrogen content. The urea nitrogen values were determined by the micro-aerofiltration method of Sobel[7]. The normal range in this laboratory is 10 to 22 mg. per 100 ml. of blood. Due to technical difficulties, it was impossible to perform total fecal nitrogen studies. The subjects who ingested the blood, however, had black, tarry stools (non-diarrheic) for 3 to 5 days.

One week later, the above study routine was repeated on the same 3 subjects, but this time a single meal of a protein concentrate preparation*, equivalent to 180 gm. of protein, was administered instead of blood. The same studies were performed on subjects C, D and E using varying amounts of beefsteak** alone and beefsteak plus concentrate.

Results. The results of the control studies performed on these normal subjects before the experiment was started are tabulated in Table 1. All the values are normal and there is no evidence of impaired renal function.

Figure 1 demonstrates the blood urea nitrogen curves obtained after the ingestion of 800 ml. of whole blood (equivalent to 180 gm. of protein) by subjects A, B and C. The maximum elevations of the blood urea nitrogen were 4, 5 and 7 mg. per 100 ml. (25 to 35% increase) above the basal fasting level. These rises occurred at approximately 5 hours after the ingestion of the blood and fell to normal levels within the 24 hours of the experimental period.

After the ingestion of 180 gm. of protein concentrate (as 293 gm. of Protinal) by the same subjects A, B and C, the urea nitrogen figures rose 19, 20 and 21 mg. per 100 ml. (100 to 119% increase) above the fasting levels, as shown in Fig. 2. These maximum ele-

TABLE 1.—RESULTS OF CONTROL STUDIES ON 5 NORMAL SUBJECTS

Subject	*A*	*B*	*C*	*D*	*E*
Weight, kg.	67.3	89.1	69.1	67.3	80.0
Age, years	27	39	25	28	25
Blood pressure mm. Hg	110/60	134/80	110/70	124/76	120/80
Urinalysis	neg.	neg.	neg.	neg.	neg.
Blood urea nitrogen mg./100 ml.	19	18	15	19	22
Creatinine mg./100 ml.	1.4	0.8	0.8	1.4	1.0
Urea clearance % of normal	130	132	136	98	136

*Protinal was the protein concentrate employed and was kindly supplied by the National Drug Co., Philadelphia, Pa. This preparation contained 18.4 gm. of the protein concentrate per 30 gm. of mixture; 293 gm. of Protinal, equivalent to 180 gm. of protein, were mixed with water in a Waring Blender before administration.

**Lean beefsteak which contained 172 gm. of protein per kilogram was used.

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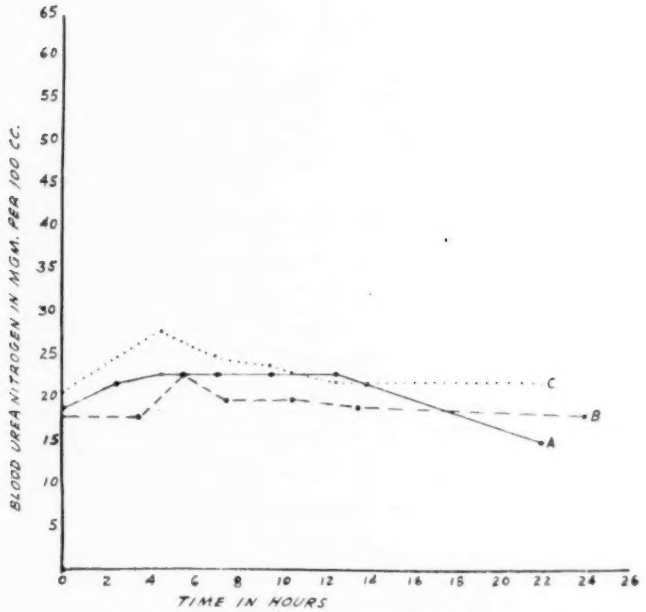
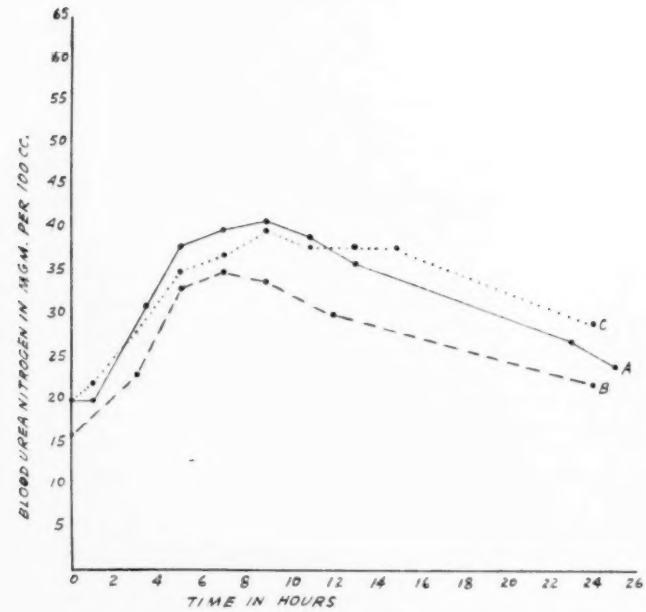


BLOOD UREA NITROGEN CURVES OBTAINED AFTER INGESTION OF 800 C.C. OF WHOLE BLOOD (EQUIVALENT TO 180 GMS. OF PROTEIN) BY SUBJECTS A, B AND C.

Fig. 1.

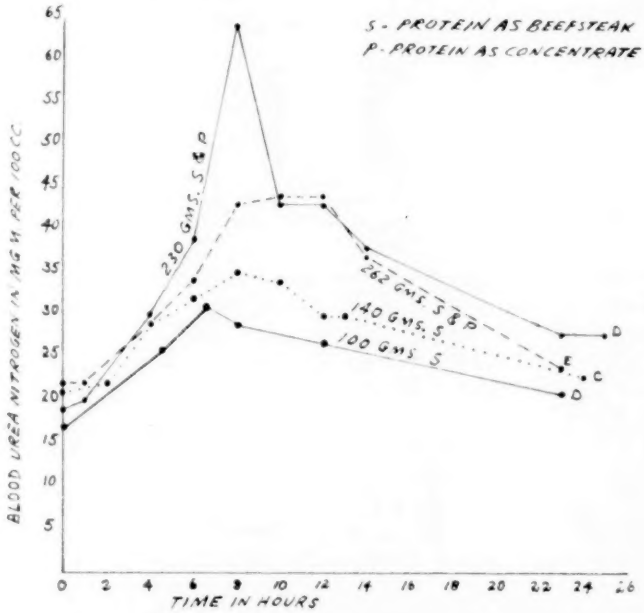


BLOOD UREA NITROGEN CURVES AFTER THE INGESTION OF 180 GMS. OF PROTEIN CONCENTRATE (AS 293 GMS. OF PROTINA) BY SUBJECTS A, B AND C.

Fig. 2.

vations occurred 7 to 9 hours after ingestion of the concentrate and although the values declined, they did not return to the basal levels in 24 hours.

After the ingestion by subjects C, D and E of from 100 to 262 gm. of protein, either as beefsteak alone or supplemented with protein concentrate, the urea nitrogen values rose 14 to 45 mg. per 100 ml. above the basal level



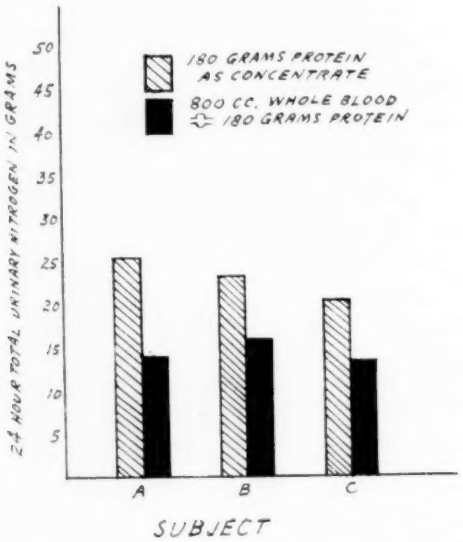
BLOOD UREA NITROGEN CURVES OBTAINED AFTER INGESTION BY SUBJECTS C, D AND E OF FROM 100 TO 262 GMS. OF PROTEIN AS BEEFSTEAK ALONE OR SUPPLEMENTED WITH PROTEIN CONCENTRATE.

Fig. 3.

(67 to 237% increase). As can be observed from Fig. 3, the maximum urea nitrogen elevations occurred 6½ to 10 hours after ingestion and were directly related to the amount of protein eaten. The values did not reach the basal levels after 24 hours.

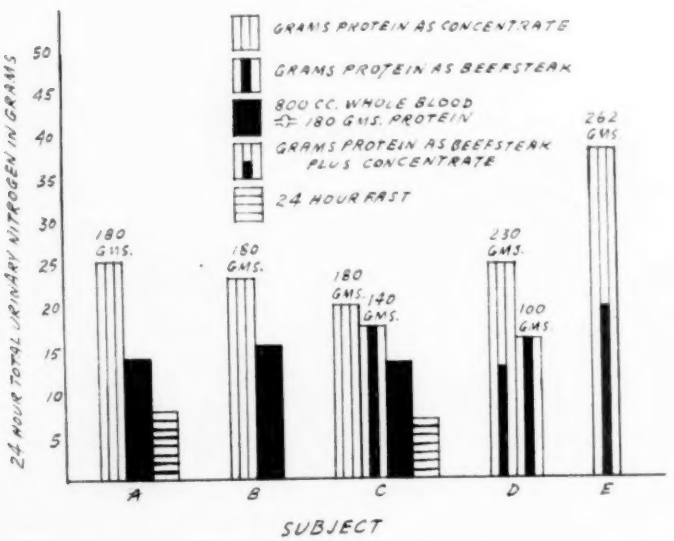
Figure 4 contrasts the 24-hour urinary nitrogen excretion after ingestion of 800 ml. of whole blood and after 180 gm. of protein concentrate (subjects A, B and C). The levels of urinary nitrogen were approximately twice as great for protein concentrate as for the equivalent amount of blood protein.

Figure 5 represents the urinary nitrogen excretion in all 5 subjects after the ingestion of varying amounts of protein as concentrate or beefsteak or both, and as 800 ml. of blood. The 24-hour total nitrogen excretion is directly proportional to the amount of concentrate or beefsteak, or both, taken into the gastrointestinal tract. The protein of blood does not appear to be absorbed from the gastrointestinal tract as readily as the other proteins used. There is, however, sufficient absorption to increase the 24-hour urinary nitrogen



24 HOUR URINARY EXCRETION AFTER INGESTION OF 800 c.c. OF WHOLE BLOOD AND AFTER 180 Gms. OF PROTEIN CONCENTRATE BY SUBJECTS A, B AND C.

Fig. 4.



URINARY NITROGEN EXCRETION IN ALL 5 SUBJECTS AFTER THE INGESTION OF VARYING AMOUNTS OF PROTEIN AS CONCENTRATE AND/OR BEEFSTEAK AND AS 800 c.c. OF BLOOD.

Fig. 5.

excretion over the basal level during a 24-hour fast (subjects A and C).

Discussion. The ingestion of 800 ml. of whole human blood by normal adult, healthy males produced only a slight rise in the blood urea nitrogen concentration. Greenblatt and Cohn demonstrated that after venesection and autoingestion of a similar quantity of blood, a marked drop in urea clearance occurred and a significant azotemia resulted. The present study would tend to substantiate their postulate that impaired renal function resulting from a reduction in the circulating blood volume is the basic factor in the development of the azotemia.

The ingestion within 30 minutes of 239 gm. of protein concentrate (quantitatively equivalent to 180 gm. of protein in 800 ml. of whole blood) resulted in significant elevations of the blood urea nitrogen values greater than those obtained by Greenblatt and Cohn after venesection. The maximal rise with protein concentrate occurred in 7 to 9 hours; the maximal rise with blood after venesection occurred after 24 hours. This would indicate that the primary mechanism for azotemia in these studies is different. It results directly from absorption and metabolism of the protein in the former case, and primarily from impaired renal function in the latter, as indicated by the maximum reduction of the urea clearance in 24 hours.

It appears that blood is not absorbed from the bowel as readily as the beefsteak or protein concentrate. The 24-hour urinary nitrogen and maximum blood urea nitrogen values were significantly less for blood than for equivalent amounts of the other proteins used. The maximum blood urea nitrogen and 24-hour urinary nitrogen values obtained for the varying amounts of beefsteak and protein concentrate were directly proportional to the amount of protein ingested and independent of type. As little as 100 gm. of protein, as beefsteak, produced a greater maximum blood urea nitrogen and 24-hour urinary nitrogen level than 180 gm. of blood protein.

This study is actually a control for the previous conflicting experimental observation in the literature and demonstrates the differences in absorption and metabolism between blood and other proteins from the gastrointestinal tract. It appears that the *time* of occurrence of the maximum blood urea nitrogen elevation is significant in the interpretation of the data. A similar experiment was performed by Gregory *et al*[3]. They fed blood and various types of proteins to dogs. The present findings parallel their results, including the time of the blood urea nitrogen elevation. The rise with fed blood was higher in the dogs than in humans. This may have been due to the fact that more blood per kilogram was fed to the dogs. The present data practically duplicate the previous results.

It may be possible to reconcile the divergent opinions concerning the mechanism of the azotemia. Yuile and Hawkins fed blood fractions to mongrel dogs and observed the peak of the blood urea nitrogen levels early, between 4½ and 10 hours. They failed to bleed their dogs and assumed that the azotemia resulted from absorption of the blood fractions. The present experimental data likewise demonstrated maximal blood urea nitrogen figures between 4½ and 10 hours after blood ingestion. This was also directly due to protein absorption from the blood in the intestine. Kaump and Parsons[5] bled their dogs and fed them their own blood. They noted a maximum blood urea nitrogen rise after 24 hours. Greenblatt and Cohn made the same observations in their human subjects. It would thus appear that blood,

placed directly into the gastrointestinal tract, in the absence of hemorrhage, produced a slight but maximal urea nitrogen elevation before 10 hours. In the presence of severe hemorrhage the peak rise occurred after 24 hours, due primarily to a contracted blood volume with resultant impairment of renal function. Schiff and his co-workers reported maximum urea nitrogen elevations within 12 hours after 1,000 ml. whole blood feedings. These elevations were significantly higher than those observed in the present experiment. Their patients, however, were in an older age group. Some of them were hypertensive, while others had diminished urea clearances. The early presence of significant azotemia seems to indicate that the peak rise was due to absorption of blood protein causing overloading of the kidneys which may have had some pre-existing degree of renal damage.

It appears from our studies that protein from ingested blood is very poorly absorbed. Protein from protein concentrate or steak is very easily absorbed and metabolized and raises the blood urea nitrogen to high levels. The urinary excretion of nitrogen is proportional to the amount of protein absorbed. The increase in urinary nitrogen is small when due to the absorption of blood proteins from the intestine, and it is large when equivalent amounts of protein as protein concentrate or steak are present in the gastrointestinal tract. Thus, when there is a marked elevation of the blood urea nitrogen from gastrointestinal hemorrhage, diminished renal excretion with nitrogen retention must be present. This is due to either pre-existing renal damage or impaired renal circulatory dynamics. It might incidentally be noted that high protein feedings, such as the Meulengracht diet, would contribute largely to the azotemia and would cause a greater degree of urea nitrogen elevation than would fasting or the feeding of fat or carbohydrate. This does not imply disapproval of the Meulengracht diet, but indicates that the level of the azotemia, in bleeding patients on such a diet, is not necessarily a measure of the severity of the hemorrhage.

Summary and Conclusions. 1. In healthy adult males, a single feeding of a large quantity of whole blood produces a small rise in the blood urea nitrogen. The peak rise occurs early, within 12 hours.

2. Single equivalent protein feeding of beefsteak or protein concentrate, or both, to the same subjects produces a large rise in the blood urea nitrogen. The peak rise also occurs early, within 12 hours.

3. In both instances the azotemia appears to be dependent upon the degree of absorption and metabolism of the ingested proteins. The protein of whole blood is not absorbed as readily as beefsteak or protein concentrate.

4. The quantitative 24-hour urinary nitrogen excretion is directly proportional to the degree of absorption and metabolism of the ingested protein. This value is much lower for ingested blood than for other proteins.

5. The important factors in the azotemia of gastrointestinal hemorrhage are: a) The size of the hemorrhage: After venesection and ingestion of a critical amount of whole blood, a significant rise in the blood urea nitrogen develops and a marked fall in urea clearance occurs. The peak rise depends upon exceeding the critical level for blood loss, thus producing a contracted blood volume with diminution in renal excretory function. b) Preexisting renal disease: This will be aggravated by an even smaller compromise of the circulation and may cause the peak blood urea nitrogen rise to occur earlier (within 12 hours). c) Protein feeding: This may serve as a

large source for early elevation of the blood urea nitrogen. If the renal excretory function is impaired, the absorption of ingested protein food from the gastrointestinal tract will contribute greatly to the azotemia.

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SUMMARIO E CONCLUSIONES IN INTERLINGUA

Inducite Azotemia in Humanos post Ingestion Massive de Proteina e Sanguine e le Mechanismo de Azotemia in Hemorrhagias Gastrointestinal

1. In masculos adulte in bon stato de valetude, un ingestion unic de grande quantitates de sanguine integre produce un parve augmento in le nitrogeno del urea sanguinee. Le culmine del augmento es tosto attingite, *i.e.* intra 12 horas.

2. Un equivalente ingestion unic de proteina in le forma de beefsteak o concentrato proteinic o de un combination de ambes produce in le mesme individuos un grande augmento in le nitrogeno del urea sanguinee. Etiam hic le culmine del augmento se attinge tosto, intra 12 horas.

3. In ambe casos le azotemia depende apparentemente del grado de absorption e metabolismo del proteina ingerite. Le proteina de sanguine integre non es absorbite tanto facilemente como le proteina de beefsteak o concentrato proteinic.

4. Le quantitate del excretion urinari de nitrogeno intra 24 horas es directemente proportional al grado de absorption e metabolismo del proteina ingerite. Iste valor es multo plus basse pro sanguine ingerite que pro altere proteinas ingerite.

5. Le factores importante in le azotemia de hemorrhagia gastrointestinal es le sequente: (a) Le dimensiones del hemorrhagia. Post venesection e ingestion de un critic quantitate de sanguine integre, il occurre un significative augmento in le nitrogeno del urea sanguinee e un marcate reduction del clearance de urea. Le culmine de ille augmento in le nitrogeno del urea sanguinee depende del perdita de sanguine, *i.e.*, del exceder, per iste perdita, de un definite nivello critic, resultante in un contrahite volumine sanguinee con diminution del function excretori renal. (b) Pre-existente morbo renal. Isto es aggravate per un ancora plus parve compromisso del circulation e pote effectuar un plus rapide attingimento del culmine del augmnto de nitrogeno del urea sanguinee, *i.e.*, un attingimento de ille culmine occurrente intra 12 horas. (c) Ingestion de proteina. Isto pote functionar como un ric reservoir pro le precoce elevation del nivello de nitrogeno in le urea sanguinee. Si le function excretori renal es defective, le absorption de ingerite proteina per le tubo gastrointestinal contribue grandemente al azotemia.

HEMORRHAGIC DIATHESIS WITH INCREASED CAPILLARY FRAGILITY CAUSED BY SALICYLATE THERAPY

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Hemorrhage has been recognized as a complication of salicylate therapy since 1883[2]. Fatal cases have usually been the result of suicidal attempts[6], accidental ingestion of large doses by children[15] or daily intravenous administration of 10 gm. of sodium salicylate[1,5]. Such cases must be regarded as rarities if one considers the wide use of salicylates in the dosage commonly employed. However, several authors have reported hemorrhagic symptoms of lesser degrees, but of clinical importance after much less than 10 gm. of salicylates per day[3,14,17]. The present report illustrates 3 such instances.

Material and Methods. BLEEDING TIME was determined by the method of Ivy[8]. The maximum normal time is 6 minutes.

CLOTTING TIME OF VENOUS BLOOD. One milliliter of blood was placed in each of 3 glass tubes (75 by 8 mm.). Starting 10 minutes after venipuncture, the first tube was tilted every minute until clotted. The second tube was started when the endpoint of the first one was reached. The third tube was started when the second one was clotted. The endpoint of the third tube was recorded as clotting time of venous blood. Maximum normal time is 30 minutes.

PROTHROMBIN TIME was performed by the method of Quick[10]. The normal range is 13 to 15 seconds.

RECALCIFICATION TIME. This was the time between the addition of 0.1 ml. of 1/40 M $CaCl_2$ solution to 0.1 ml. of oxalated plasma and the appearance of a clot. The maximum normal time is 180 seconds.

THE PLATELET COUNT was determined by the method of Rees and Ecker[12].

CAPILLARY FRAGILITY was estimated by the Rumpel-Leede test[16].

CLOT RETRACTION was noted by observation of the clot incubated at 37° C. for 12 hours.

FIBRINOGEN was determined by the method of Ratnoff[11].

THROMBIN TIME. The time interval between the addition of 0.1 ml. of a standardized thrombin solution to 0.1 ml. of oxalated plasma and the appearance of a clot was the thrombin time. The thrombin solution was standardized to give a normal time of 23 to 28 seconds.

PROTHROMBIN CONSUMPTION TEST. Two milliliters of blood were placed in a dry glass tube of 75 by 8 mm. and incubated at 37° C. Two hours after venipuncture 0.1 ml. of the supernatant serum was added to a mixture of 0.1 ml. of normal $BaSO_4$ treated plasma (used as fibrinogen substrate), 0.1 ml. of thromboplastin solution and 0.1 ml. of 1/40 M $CaCl_2$ solution. The time interval between the addition of serum and the appearance of a clot is the serum prothrombin time. Normal values exceed 25 seconds.

Normal $BaSO_4$ treated plasma. One hundred milligrams of $BaSO_4$ were added to each milliliter of normal oxalated plasma. The mixture was gently shaken at room temperature for 5 minutes and the $BaSO_4$ centrifuged out at 2000 r.p.m. for 10 minutes.

Case Reports. CASE 1. A.P., a 48-year-old housewife, was admitted to the University of Minnesota Hospitals for a breast biopsy. At the time of surgery on May 9, 1955, the blood loss was more marked than one would usually expect with such a procedure. The histologic report of the frozen section was "intraductal papilloma." Because of the excessive bleeding it was decided to defer mastectomy. Postoperatively blood oozed for several days from the incision and a large hematoma surrounded the wound. Tests of hemostasis performed on May 10, 1955, are presented in Table 1. The only abnormalities were a prolonged bleeding time and a positive Rumpel-Leede test. The past history revealed that the patient had had rather severe menorrhagia from 1948 to 1951. Several curettages were of no diagnostic value and in 1951 it was finally decided to

perform a hysterectomy. The uterus revealed no abnormalities to account for the bleeding. The operation was uneventful. The patient had also noticed that she bruised easier and bled longer after cuts since 1948. After more intensive questioning it was disclosed that the patient had been taking from 4 to 8 aspirins a day for arthralgia since 1948. Suspecting that this may have been the offending agent, the drug was stopped on May 11, 1955, and a repetition of the tests of hemostasis 8 days later revealed no abnormalities. A simple mastectomy was performed on May 20, 1955, without any hemorrhagic complications.

COMMENT. The onset of hemorrhagic symptoms with the beginning of a self-prescribed maintenance dose of aspirin in 1948 is strong circumstantial evidence that bleeding and salicylate therapy were related. It is of interest that the patient remembered that she did not take any aspirin during the hospitalization for the last curettage and the subsequent hysterectomy in 1951. This probably accounts for the uneventful hysterectomy. While hospitalized for the breast biopsy she kept on taking aspirin out of her own supply. The return of the abnormal tests of hemostasis to normal after discontinuing the drug and the uneventful mastectomy strongly indicate that the patient's hemorrhagic symptoms were induced by salicylates.

CASE 2. C.O., a 66-year-old housewife, was transferred to the University of Minnesota Hospitals on February 1, 1955, two weeks after an episode of hematemesis which was successfully treated with blood transfusions in another hospital. The patient had no premonitory gastrointestinal symptoms and had never been bothered by any digestive troubles in the past. For approximatively 20 years the patient had been taking aspirins intermittently for arthritis. She was also known to bruise easily for several years; the onset of this symptom could only be approximated. The patient remembered that she did not bruise easily in her youth and during adult life when she had her children. Positive physical findings were limited to a minimal degree of rheumatoid arthritis. Radiologic studies of the gastrointestinal tract were negative. A gastroscopic examination revealed only a few patches of atrophic mucosa. The maximum degree of free gastric acid after histamine stimulation was 52. Total acidity was 68 degrees. Hepatic function tests were normal. The tests of hemostasis on February 1, 1955, were all within normal limits (Table 2). It should be stressed that the patient had taken aspirins (0.3 gm., 6 times daily, on the average) up to the episode of hematemesis on January 17, 1955, but had stopped the drug thereafter. A test dose of enteric coated aspirins (0.6 gm., 3 times daily) was given for 4 days and the tests of hemostasis were repeated thereafter. The Rumpel-Leede test became markedly positive. The bleeding time was not prolonged, but its interpretation is open to question because of the development of a subcutaneous hematoma at the site of

TABLE 1.—STUDIES OF HEMOSTASIS IN CASE 1, A.P.

	May 10, 1955 Patient on Aspirin Therapy	*May 19, 1955 Patient off Aspirin Therapy for 8 Days*
Bleeding time (min.)	8*	5
Clotting time (min.)	25	23
Prothrombin time (sec.)	14.8	13.6
Recalcification time (sec.)	150	150
Platelets (per c.mm.)	153,000	162,000
Rumpel-Leede test	Positive	Negative
Clot retraction	Normal	Normal
Fibrinogen (mg. per 100 ml.)	410	400
Thrombin time (sec.)	23.0	23.0
Prothrombin consumption, serum prothrombin time 2 hrs. after venipuncture (sec.)	33.2	29.2

* Development of subcutaneous hematoma at the site of skin-puncture.

skin-puncture within 30 seconds after performing the puncture. This observation has actually diagnostic importance, because the development of this type of hematoma is a frequent occurrence in bleeding time determinations on individuals with either thrombocytopenia or congenital familial increased capillary fragility (van Willebrand's disease). Since the platelet count was normal, one has to assume that this phenomenon was the result of increased capillary fragility.

occasionally occurs without demonstrable pathology or drug therapy. It is probable, however, that aspirin induced some degree of gastric irritation and a defect of hemostasis which both played an etiologic rôle. Ulcerations of gastric mucosa have been reported after salicylate therapy[7], but in the present case they could not be demonstrated.

TABLE 2.—STUDIES OF HEMOSTASIS IN CASE 2, C.O.

	February 1, 1955 Patient off Aspirin Therapy for 2 Weeks	*February 4, 1955 Patient on Aspirin Therapy for 4 Days*
Bleeding time (min.)	2	4*
Clotting time (min.)	19	21
Prothrombin time (sec.)	15.0	14.4
Recalcification time (sec.)	150	120
Platelets (per c.mm.)	214,000	212,000
Rumpel-Leede test	Negative	Positive
Clot retraction	Normal	Normal
Fibrinogen (mg. per 100 ml.)	360	390
Thrombin time (sec.)	28.0	24.5
Prothrombin consumption, serum prothrombin time 2 hrs. after venipuncture (sec.)	37.9	44.4

* Development of subcutaneous hematoma at the site of skin-puncture.

TABLE 3.—STUDIES OF HEMOSTASIS IN CASE 3, R.B.

	December 12, 1954 Patient on Aspirin Therapy	*December 20, 1954 Patient off Aspirin Therapy for 8 Days*	*December 27, 1954 Patient on Aspirin Therapy for 7 Days*
Bleeding time (min.)	2*	2	3*
Clotting time (min.)	20	24	24
Prothrombin time (sec.)	17.5	15.0	15.0
Recalcification time (sec.)	100	150	150
Platelets (per c.mm.)	250,000	212,000	204,000
Rumpel-Leede test	Positive	Negative	Positive
Clot retraction	Normal	Normal	Normal
Fibrinogen (mg. per 100 ml.)	325	..	..
Thrombin time (sec.)	24.0	23.0	23.0
Prothrombin consumption, serum prothrombin time 2 hrs. after venipuncture (sec.)	40.5	45.2	55.0

* Development of subcutaneous hematoma at the site of skin-puncture.

COMMENT. There is little doubt that in this patient aspirin induced a positive Rumpel-Leede test and a qualitative abnormal bleeding time. The question whether the episode of hematemesis was secondary to salicylate therapy cannot be answered with certainty, because it is well known that hematemesis

CASE 3. R.B., a 66-year-old retired salesman, had been confined to a wheelchair for 20 years for a crippling rheumatoid arthritis. The mainstay of his therapy was aspirin, of which he took from 8 to 10 tablets (0.3 gm. each) a day. During the fall and winter of 1954 the patient had several episodes of epistaxis which necessitated the transfusion of 1500 ml. of blood in an outside hospital. In November, 1954, he had melena for 3

days. The admission to the University of Minnesota Hospitals on December 11, 1954, was prompted by a new episode of severe epistaxis. It was not possible to localize any bleeding point and, despite anterior and posterior nasal packs, the patient had to be given 2000 ml. of blood. Except for a severe rheumatoid arthritis the physical examination was negative. The patient was normotensive. Tests of hemostasis on admission revealed a positive Rumpel-Leede test and a minimal prolongation of the prothrombin time (Table 3). An ecchymotic area developed at the site of skin-puncture performed for the determination of the bleeding time. Aspirin therapy was immediately discontinued and 9 days later on December 20, 1954, all tests of hemostasis had reverted to normal. The patient was then restarted on enteric coated aspirins (0.3 gm., 4 times per day). Seven days later the Rumpel-Leede test had become positive and several bleeding time determinations, though not prolonged, were all complicated by the development of a subcutaneous hematoma at the site of skin-puncture. The prothrombin time remained unchanged. Radiologic studies of the gastrointestinal tract revealed a few diverticula in the sigmoid colon. Liver function tests were normal.

COMMENT. This patient developed hemorrhagic symptoms after many years of continuous salicylate therapy. He is the only case with a mild prolongation of the prothrombin time. The return of all tests of hemostasis to normal after stopping aspirin and the induction of the abnormal Rumpel-Leede test and bleeding time upon resumption of therapy, is adequate proof for the etiologic rôle of the drug.

Discussion. The pathogenesis of salicylate induced hemorrhagic symptoms has practically always been attributed to its prothrombin depressing activity. That salicylic acid and its salt have a prothrombopenic effect has been demonstrated beyond doubt in the experimental animal[9] and in human beings[13]. More recent experiments have also shown that there is an associated depression of the stable prothrombin conversion factor[4]. However, a pronounced effect on these clotting factors is only observed with large and repeated doses of salicylates. The degree of prolongation of the prothrombin time occasionally encountered with commonly used doses of these drugs is usually not sufficient to account for the bleeding. Another disturbance of the mechanism of hemostasis had to be implicated, therefore, to account for the hemorrhagic diathesis in patients who are on small doses of salicylates and who do not show any changes in the prothrombin time. The 3 cases presented above leave little doubt that aspirin therapy induced increased capillary fragility. It is rather surprising that only very few authors[6,14,17] have suggested an untoward effect of salicylates on the capillaries. The fact that with the widespread use of these drugs only few patients develop complications is a very fortunate one and suggests that the development of increased capillary fragility to aspirin is a matter of individual sensitivity. For control purposes we have tested 20 patients on prolonged salicylate therapy and were unable to find any abnormalities of either the Rumpel-Leede test or the bleeding time. A mild prolongation of the prothrombin time was encountered 5 times without any hemorrhagic symptoms. Elevated fibrinogen levels, as in patients A.P. and C.O., were probably related to the underlying rheumatoid disease.

The observations reported above emphasize the need to consider salicylates as possible offending agents in any case of unexplained acquired hemorrhagic diathesis.

Summary. 1. Three patients have been presented who developed hemorrhagic symptoms while on aspirin therapy. All of them had a positive Rumpel-Leede test and an abnormal bleeding time. Only one case showed a minimal prolongation of the prothrombin time.

2. Interruption of salicylate therapy was followed by a normalization of all

tests of hemostasis. Resumption of the drug in two cases reinduced the abnormal bleeding time and the positive Rumpel-Leede test.

3. It is believed that salicylate therapy increased capillary fragility and was the major, if not the only, cause of the acquired hemorrhagic diathesis.

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SUMMARIO IN INTERLINGUA

Diathese Hemorrhagic con Augmentate Fragilitate Capillar, Causate per Therapia a Salicylato

1. Es presentate tres patientes qui disveloppava symptomas hemorrhagic durante un curso therapeutic a aspirina. Omnes habeva un reaction positive in le test de Rumpel-Leede e un anormal tempore de sanguination. Solmente un del casos monstrava un minime prolongation del tempore prothrombinic.

2. Le interruption del therapia a salicylato esseva sequite per le normalisation de omne tests de hemostase. In duo casos le recomenciamento del therapia re-induceva le anormal tempore de sanguination e le reaction positive in le test de Rumpel-Leede.

3. Nos opina que le therapia a salicylato augmentava le fragilitate capillar e esseva le major si non le sol causa del acquirite diathese hemorrhagic.

THE INTERACTING EFFECTS OF PUBLIC HEALTH, FERTILITY BEHAVIOR AND GENERAL ECONOMY ON STANDARDS OF LIVING: IV. CHARACTERIZATION OF THRESHOLDS AND STAGES OF DEVELOPMENT IN THE BIOECONOMIC MECHANISM

By Alexander Langer, M.D.

and

Paul S. Henshaw, Ph.D.*

In Papers I, II and III of this series, a methodology was developed for numerical comparison of levels of living in different countries and territories and for evaluation of various key determinants. The methodology then was used as a means for identifying countries and territories with similar problems, and for designating the character and magnitude of changes required to achieve different amounts of improvement. It is the aim of this paper to consider the mechanism by which progress is made from one level to another, to recognize turning points along the way, and to give fuller interpretation to the Country Situation Index formula as a model.

In the previous papers, a Situation Index value was obtained for each of 70 countries and territories (for which data are available) which gives indication of progress made. By systematic arrangement of the countries and territories according to Situation Index values, a scale of development was obtained with the more advanced countries at the top and the less advanced at the bottom. The range thus set off can be regarded as the pathway of *bioeconomic progress,* and the process which operates to cause rise or fall on the scale can be treated as a mechanism and analyzed.

RECOGNITION OF THRESHOLDS AND STAGES OF DEVELOPMENT. Previously, we have taken cognizance of progress in terms of three elements: food intake, industrial energy consumed, and income, all on a per capita basis. These elements, as made evident previously, represent in a general way the agricultural, industrial and economic productivity of the people in each instance. As emphasized, each by itself can be taken as a measure of progress, and a combination of the three can be taken as a more stable and more representative measure. We have, then, besides the over-all Situation Index (S.I.) scale, the scales for caloric intake (C), industrial energy consumed (E) and income (I), by means of which turning points can be identified and characterized. Because of its underlying importance, caloric intake will be considered first. The procedure will be to develop on an *a priori* basis a picture of thresholds and stages in the bioeconomic process and after that to derive representative values for different components as they apply at different levels.

In picturing the process of bioeconomic development, it is logical to begin with biological features. Underlying all living activity are the dominant instincts for self preservation and species preservation. Subsistence is a requirement for both. When per capita food intake drops below a certain level, starvation occurs. Accordingly, as a basis for life itself, we can at the outset rec-

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ognize a *threshold of subsistence*, a level of nutrition required for the existence of life. Mere survival, however, does not in itself provide entirely favorable conditions for expression of the second instinct, reproduction, as it is known from a significant amount of animal experimentation and from practical experience with human beings, that fertility (fecundity) is lower among the undernourished. It may be assumed, therefore, that as caloric intake rises above the minimum required for the existence of life, a *threshold of full fertility potential* is reached.

As part of the struggle for survival, there is also the matter of health. Undernourished and underprivileged peoples are more vulnerable to disease inasmuch as their natural resistance is lower and inasmuch as such people are less able to avail themselves of the health and medical services with which natural resistance can be supplemented. We may therefore postulate both a threshold of full natural resistance and a *threshold of full health potential*, the first being attained mainly by nutritional improvements and the second, in part, at least, by this means. Since the development of natural resistance and the development of full health are overlapping processes and cannot be distinguished easily, we shall concern ourselves here only with the latter.

In addition to the underlying instincts for survival and reproduction, which characterize all living species, there is the more strictly human feature of aspirations for cultural development: the desire to learn, to develop talents, to accomplish ambitions, and to live with comfort and luxury, including desire for improvements in health. In the human species, struggle for cultural development occurs almost as naturally as struggle for individual and group survival.

Beginning thus to characterize the mechanism of bioeconomic development, we have at the lowest operating level a process which is almost entirely biological, since the ability to survive and reproduce is governed much more by conditions of nutrition than by other types of regulating factors. With respect to the most primitive situation, therefore, we can say that opportunity to fulfill the elemental biological requirements for life varies directly with availability and use of food, and accordingly that progress up to a point approaching full fertility can be measured in such terms.

Going forward from the point of full fertility, progress is in terms of cultural development as well as improvements in nutrition. Since, however, cultural advancement goes hand in hand with further improvements in nutrition, food intake in this range continues to be representative of progress. Actually, it continues to be representative as food consumption and cultural development change from the necessity to the comfort to the luxury categories, and extends to the point of maximum caloric intake. Food production beyond the amounts consumed results in surpluses, and, as such, have meaning only in economic terms. On the nutritional scale, therefore, we can recognize along with the other points visualized, one where food consumption begins to include excess or luxury components as well as the component needed for full health, also a point where food consumption becomes a maximum. For reasons which will become more apparent below, these points will be called the *threshold of stable living* and the *threshold of exclusive economic gains*, respectively.

Before going on to deal with other features, the idea of a threshold of stable living needs further elucidation. In order to say that food consumption is in the excess or luxury category, it

is necessary to classify such consumption as not needed for the primary functions of life, such as maintenance and reproduction. This brings us back to health, making it necessary to designate the threshold of full health potential and the threshold of excess or luxury food consumption as occurring at the same level. Thinking also of the cultural changes that occur along with the attainment of full health and a condition of living that permits the consumption of some foods on a luxury basis, it is appropriate to regard this same point as the threshold of exclusive cultural development, since health is no longer a problem. Due to the fact that there is opportunity at this stage for cultural development and some luxury living at the same time, life under these conditions can be, and obviously is, more stable.

As part of the development governed primarily by biological or nutritional conditions, it is important to take note also that as improvements in level of living reach and go beyond the threshold of full fertility potential, and there is increasing opportunity to satisfy the natural and usual desires for achievements and comforts, activities in connection with the latter compete, as it were, for the energies ordinarily devoted to reproduction, causing birth rates to become reduced. Reduction in fecundity has been observed sufficiently often in connection with economic improvement, particularly industrialization, that the change has been referred to commonly as the *demographic transition*. Keeping in mind that increase in caloric intake and social development go along together, it is conceivable that a turning point is reached in the development process where a population is sufficiently well off to satisfy the primary desires for health and cultural status and to have more children at the same time. There are but few instances, however, indicating that such a course is followed.

In the description to this point, one significant feature has been passed over. This is the matter of death rates. With improvements in health, death rates decline, reaching a minimum in the range of 1.0% per year. The point at which death rate decline reaches a minimum we shall call the *threshold of stable death rates*, which as will be indicated below, appears to occur in advance of the other manifestations of full health potential.

Associating the various turning points in sequential order, as visualized, we have in effect a *grid of thresholds*, defined mainly in biological terms and based on nutrition, the most fundamental requirement for the existence of life (Fig. 1). The features occur in order as follows: threshold of subsistence, threshold of full fertility potential, threshold of stable death rates, threshold of full health potential (or of stable living), and threshold of exclusive economic gains (point of maximum caloric intake). Between each threshold is a zone or stage of development, each of which has a specific significance. But, before dealing with these, it is important to consider other grids, those that can be based on industrial energy consumed and income.

With respect to income, or purely economic gains, it is possible to visualize a scale of privileges which occur along with increasing remuneration. There is but one, however, which has particular usefulness here. This is the opportunity for saving and investment. On a population group basis, saving becomes an entity only when per capita productivity in terms of food and other basic commodities becomes greater than *unity;* that is, when each person on the average receives more than is needed for satisfying his own requirements for full health and for providing

the primary cultural opportunities. We shall refer to this point as the *threshold of country-wide savings and investment*, or in other wording, as the threshold of accelerating per capita gains, since

In relation to the caloric scale of advancement, the threshold of country-wide savings and investment would coincide with the threshold of excess food consumption, since it is only at

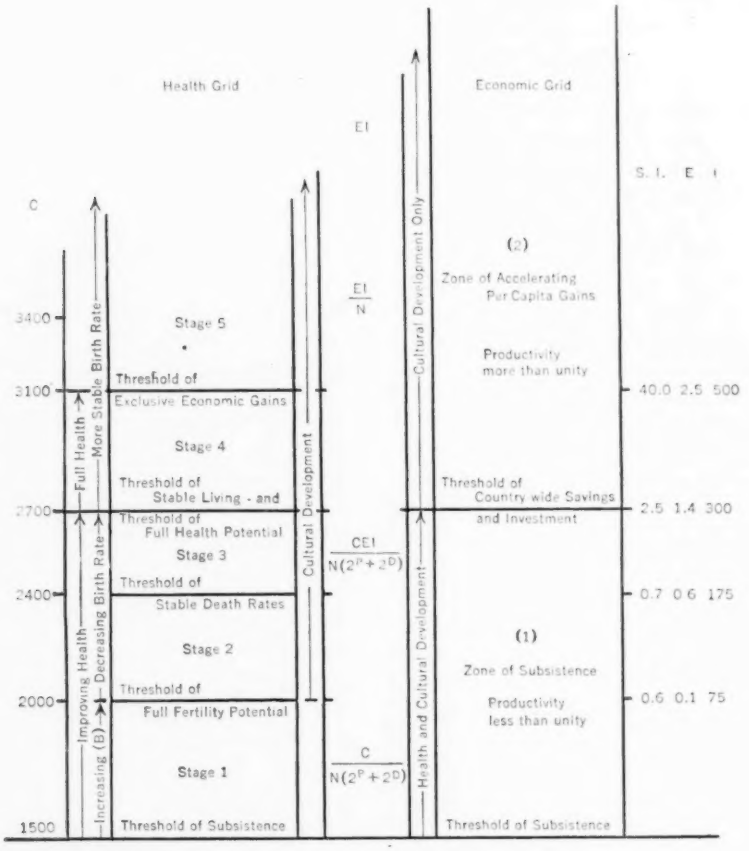

Fig. 1.—Bioeconomic development. *B*, crude annual birth rates in %; *D*, crude annual death rates in %; *P*, crude annual population increase rates in % (*B*–*D*); *N*, inhabitants per km²; *C*, daily caloric intake per person (divided by 1000 when used in the formula); *E*, industrial energy consumed per person per year in tons coal equivalent; *I*, income per person per year, U. S. dollars, 1950.

productivity below this level is totally absorbed in subsistence and that above contains a portion which can be invested and itself caused to be productive, or to earn, thereby giving the feature of acceleration.

this point or above that savings and investment become a reality on the population group basis. The fact that in the case of lower levels of development, some individuals save and invest does not alter this conclusion, as the

earnings from such investments are canceled by deficit consumption on the part of other individuals whose productivity is less than unity.

With respect to industrial energy consumed, it is also possible to visualize an ascending scale of privileges that occur along with increasing industrialization. Interestingly, however, industrialization, which covers a vast gamut of technology and which affects level of living profoundly, exerts its greatest influence after the more biological and nutritional requirements for life have been satisfied. Thresholds, or limits, that have particular significance occur after considerable progress of different kinds has taken place. Industrial development, enabling as it does greater productivity, creates one of two conditions: first, an opportunity for more people to be sustained, in which case the biological or subsistence problems continue, and second, an opportunity for higher levels of living for given populations. Assuming that there are no real limits to technical developments and that it may be possible increasingly to transform common substances into food and other materials needed for life, there are but two limits of real concern. One is the amount of living space and the other is stability of the industrial structure. These are features of particular interest in the bioeconomic picture, but for the purposes here attention will be kept on earlier phases of the process.

Considering the economic and industrial aspects together, then, we have only one threshold: the threshold of country-wide savings and investment, to be used in a grid by itself or to be associated with the grid of nutritional thresholds. In Fig. 1, health and economic grids are shown together.

Turning now to the various zones or stages of development set off by the different thresholds, we shall deal first with the two zones defined by the economic grid. For purpose of distinction, the term "zone" will be used in connection with the economic grid and the term "stage" in connection with the health grid. Between the threshold of subsistence and the threshold of savings and investment on the economic grid is a rather wide range of development, characterized as we have seen by total consumption of products in providing the minimum requirements for life, leaving little or nothing for advanced cultural development such as higher education, research, social security and the like. This we shall refer to simply as the *zone of subsistence*, or Zone 1. Above the threshold of savings and investment is the extensive and essentially unlimited range which we shall call the *zone of accelerating per capita gains*, or Zone 2. Dominant among the many features of Zone 2 are the facts that productivity is greater than unity, and that there is the possibility of savings which can be used to increase earning capacity or to purchase those things which add to cultural advancement rather than mere subsistence.

By reference to Fig. 1, it is seen that progress which takes place within the range of the zone of subsistence is visualized as being identified not only by productivity which is less than unity, but also by progressive improvements of health and cultural development represented by Stages 1, 2 and 3 of the health grid. Stage 1 on the nutritional scale is defined mainly by high and increasing birth and death rates, Stage 2 by high birth and death rates with a tendency toward decline of both, and Stage 3 by a distinct decline, all occurring concurrently with improvements in health and a growing opportunity and incentive for cultural development. Similarly, it is seen that the early part of Zone 2 is visualized as

coinciding with Stages 4 and 5 on the nutritional scale. Stage 4, with continuing cultural development, is significant in terms of choices with respect to the foods available above the amounts required for full health inasmuch as these can either be consumed or used for commercial purposes. Stage 5 has meaning only as part of economic development since further increase in food supply cannot be consumed.

QUANTITATION. Thus far discussion has been entirely on an *a priori* basis. The problem now is to associate values with the different levels of development identified and to ascertain whether there is actual evidence of the stages and turning points visualized.

As a first step in dealing with these objectives, pre-war and post-war birth rate values for different countries and territories (U. N. Demographic Yearbook, 1953) were plotted against values for caloric intake per person (retail food supply as reported by the FAO in its 1952 *World Food Survey*)* (Fig. 2). In plotting, figures were used to indicate points in order that countries and territories could be identified. This was regarded as necessary since population groups vary greatly in size causing the points to have different weighting strength, and since question arises in some cases because of special information that is available.

That there is a spread in distribution of points is as would be expected, since it is known that numerous factors in addition to nutrition affect fertility and that they do so with varying intensity in different localities. Since the distribution of points for pre-war data was more regular, the best curve that could be fitted by visual means was drawn among the points and the same curve was reproduced among the points for post-war data. That there is a downward trend in the middle region followed by the tendency to form a level plateau is evident enough, but whether there is an upward trend at the beginning is not as evident, at least from the plotted points alone. A slight rise was shown, in part, because of knowledge that fecundity is lower at starvation levels.

Interestingly, no country was found to have a food intake less than 1700 calories per person per day, this value being for India (1946–50). The lowest figure we have come across among recent data is for Indochina, which was 1560 at the end of World War II. Although it is possible that groupings of people may subsist for some time on caloric levels less than 1500, it is known from various kinds of information that this level is near the point of starvation. Accordingly, for the purposes here, 1500 has been chosen as the lowest caloric level having significance in the bioeconomic process. Granting then that fecundity is low when average caloric intake is in the neighborhood of 1500 per day, it is apparent from the curves, Fig. 2, that the point of maximum birth rate is reached in the range of 2000 calories. Granting also the downward trend of birth rates beyond 2000 to 2100 calories and the tendency to establish a minimum level, the transition from the downward to the horizontal trend is so gradual that it is possible to do little more than recognize that a turning takes place in the range 2500 to 3000 calories. For the purposes here, we shall use the intermediate value of 2700, provisionally, as representative of this change. Looking at the end of the curve, it is seen that only a few countries had a caloric intake greater than 3100 (max-

*Actually, there is some doubt as to whether retail food supply is a precise representation of food consumed, but small discrepancies do not interfere with the general picturing of behavior being attempted here.

imum 3390, Ireland). We have, therefore, arbitrarily chosen 3100 as a convenient figure representing maximum caloric intake.

In order to elucidate the picture further, death rates for the same time intervals were also plotted against per capita caloric consumption (Fig. 3). As in the case of birth rates, a wide spread in distribution of points was found, and no doubt for the same reasons. It is noteworthy, however, that the widest spread occurs at the beginning in connection with countries having the lowest caloric intake, and that in general, countries having higher caloric intakes also have lower and more similar death rates at a level which is close to the maximum health achievement. Looking at the curves, including the upper one which is a duplication of the pre-war curve among the post-war points, there is some question as to whether the rise in death rates shown in the range of 2000 calories is a correct representation of trends. There is reason for expecting such a rise, however, on the grounds that infant mortality is high (as we shall see) when caloric intake is low, thus causing death rates to follow birth rates more closely. That there is death rate decline in the range of 2100 to 2400 calories followed by a fairly stable plateau is fully evident. The fact that there is a difference in level of the pre-war and post-war curves, and also that more countries with low caloric intake have lower death rates, are matters to be commented upon later. For

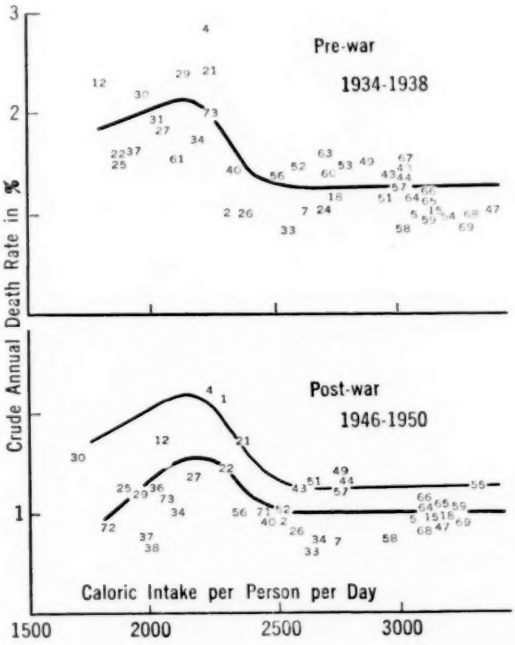

Fig. 2.—Birth rates in relation to caloric intake, different countries and territories (see Legend, Fig. 3, for identification).

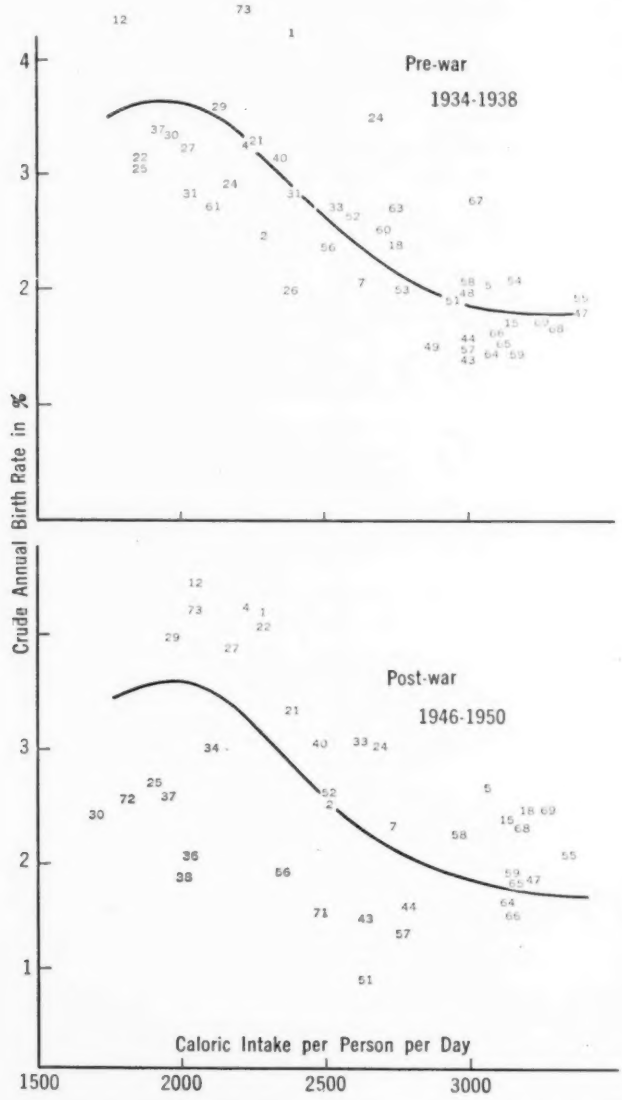

Fig. 3.—Death rates in relation to caloric intake, different countries and territories. 1 Egypt, 2 Union of S. Africa, 3 Gold Coast, 4 Mauritius, 5 Canada, 6 Costa Rica, 7 Cuba, 8 Dominican Republic, 9 El Salvador, 10 Guatemala, 11 Honduras, 12 Mexico, 13 Nicaragua, 14 Panama, 15 United States, 16, Jamaica, 17 Puerto Rico, 18 Argentina, 19 Bolivia, 20 Brazil, 21, Chile, 22 Colombia, 23 Ecuador, 24 Paraguay, 25 Peru, 26 Uruguay, 27 Venezuela, 28 Burma, 29 Ceylon, 30 India, 31 Indonesia, 32 Iraq, 33 Israel, 34 Japan, 35 Lebanon, 36 Pakistan, 37 Philippines, 38 Syria, 39 Thailand, 40 Cyprus, 41 Federation of Malaya, 42 Albania, 43 Austria, 44 Belgium, 45 Bulgaria, 46 Czechoslovakia, 47 Denmark, 48 Finland, 49 France, 50 Saar, 51 West Germany, 52 Greece, 53 Hungary, 54 Iceland, 55 Ireland, 56 Italy, 57 Luxembourg, 58 Netherlands, 59 Norway, 60 Poland, 61 Portugal, 62 Romania, 63 Spain, 64 Sweden, 65 Switzerland, 66 United Kingdom, 67 Yugoslavia, 68 Australia, 69 New Zealand, 70 Hawaii, 71 East Germany, 72 Iran, 73 Formosa.

the purposes here, we obtain the caloric value of 2400, approximately, as representative of the point at which death rates reach the more stable range.

Figures 4 and 5 show plottings of values for life expectancy and infant mortality (such as available from the 1953 Demographic Yearbook). Since these features are sometimes taken as measures of health and other cultural advancement, the trends established in relation to caloric intake are germane to the present considerations. As seen in Fig. 4, length of life becomes greater with increase in caloric intake until the maximum range of 65 to 70 years is reached, when food consumption is about 2700 calories. In Fig. 5, although the points again are rather widely scattered, the trend gives evidence that infant mortality falls as caloric intake shows improvement, reaching a low point when food consumption is 3100 calories or above. We have then the designated values of 2400 calories as the point at which death rates become stable, 2700 at which life expectancy becomes maximum, and 3100 at which infant mortality reaches a level near the vanishing point. All of these give information about the achievement of full health potential. For this particular purpose, however, infant mortality will be disregarded since it pertains to such a small portion of the total population and actually much less than 1% in the range significant to us here. From the standpoint of full health achievement, it is the level at which length of life as well as death rates become stable that is of importance. Since the findings show this to be approximately 2700, we shall employ this figure. Actually, the data presented do not permit us to distinguish with certainty between 2400 and 2700 as the point where full health potential is achieved. However, since the turning point for death rate is fairly sharp and since the results for life expectancy and also birth rate point

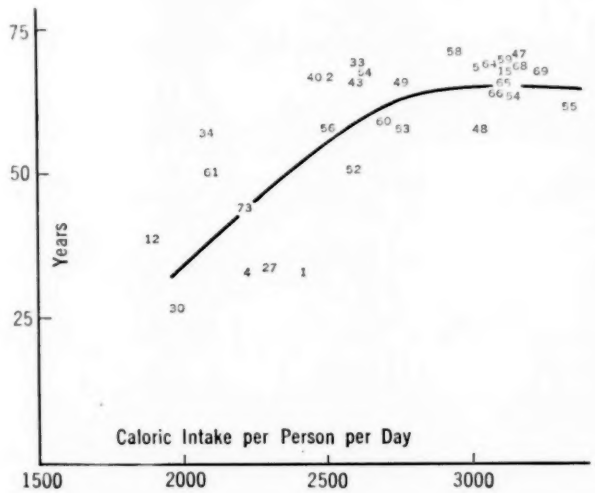

Fig. 4.—Life expectancy in relation to caloric intake, different countries and territories (see Legend, Fig. 3, for identification).

toward a figure in the range of 2700 as having significance, we shall employ both, associating particular meaning with each.

In Fig. 6, the curves for birth rate, death rate, infant mortality and life expectancy have been brought together, and turning points believed to be significant have been marked with arrows.

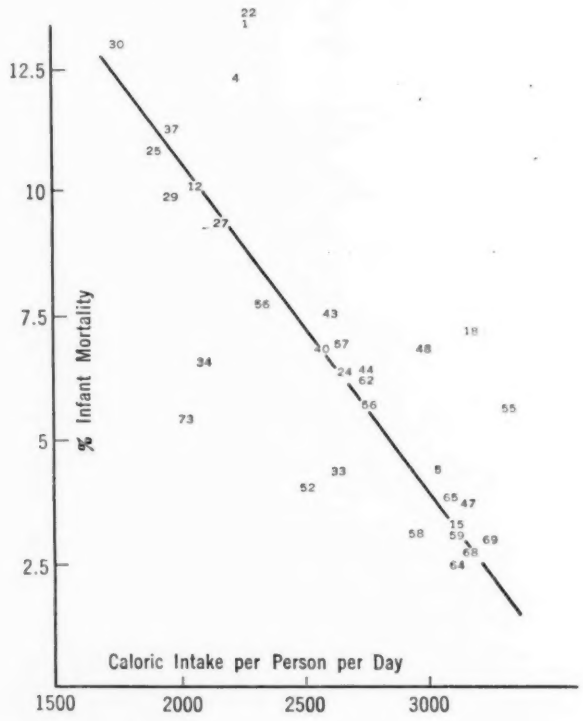

Fig. 5.—Infant mortality in relation to caloric intake, different countries and territories (see Legend, Fig. 3, for identification).

Because of the location of these points and because of the background developed in relation to them, we have aligned caloric values with thresholds as follows: 2000 with the threshold of full fertility potential, 2400 with the threshold of stable death rates, and 2700 with the threshold of full health potential (or of stable living). These values together with the more arbitrarily chosen ones of 1500 and 3100 associated with the threshold of subsistence and the point of maximum caloric intake, respectively, are shown as part of the health grid, Fig. 1.

Figure 6 also gives other information. From the trend of the curves, one obtains a clear impression of vital behavior in motion. If the caloric range 1500 to 3100 is divided roughly into thirds, the middle range is obviously one of *transition*, since birth rates, death rates and infant mortality are falling and life expectancy is rising. The pretransition range, then, is one of high birth and death rates, high infant mortality and low life expectancy, and the

post-transition range one of generally stable birth and death rates and a fairly regular life expectancy, with infant mortality approaching a level near the vanishing point. According to the background developed, health improvement is a dominant feature in the pre-transition phase, health improvement and cultural development together are dominant features in the transition phase, and cultural development alone a dominant feature in the post-transition phase.

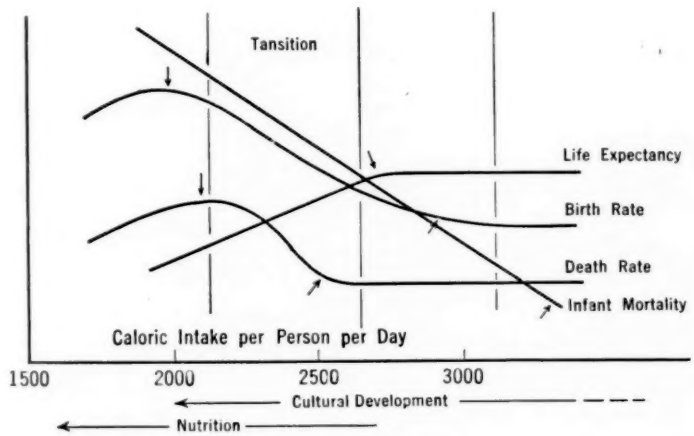

Fig. 6.—Assemblage of vital behavior curves, showing changes or turning points (arrows) in relation to caloric intake.

For purposes of fuller orientation permitting opportunity to deal with quantitative units which apply consistently throughout the entire range of bioeconomic development, it was necessary to obtain Situation Index values which tend in general to go along with the particular caloric figures obtained. In Fig. 7, Situation Index values have been plotted against values for caloric intake. Again there is a spread in distribution of points inasmuch as Situation Index values, like those for birth and death rates and for life expectancy and infant mortality, are influenced by various factors in addition to caloric intake which do not advance with complete uniformity. A curve drawn among the points to represent directional trends, however, gave opportunity to read off Situation Index values tending to be associated with the designated caloric values. The figures so obtained are shown in Fig. 1 at the right (S.I.).

Using the same procedure, values were obtained also for income (I) and for industrial energy consumed (E). These likewise are shown in Fig. 1 at the right.

The picture becomes reasonably complete, then, in terms of thresholds and stages of development as expected on the basis of general information about biologic and economic progress, and as indicated by caloric, economic, industrial and Situation Index values tending to occur along with rationally chosen stages and turning points. It is necessary to state that essentially the same impressions would have been obtained if Situation Index values had been used as the base rather than caloric values, and that such an ar-

rangement would have been more satisfactory in certain ways since it would have enabled treatment of the entire range of bioeconomic development on a single scale. We have used caloric intake, however, in order to lay stress on biological and nutritional aspects of the reaction, thus leaving a portion to be handled by other means.

Discussion and Further Analysis. Assuming that the picture set forth in Fig. 1 is generally correct, it is possible to present a more comprehensive description of the bioeconomic process.

From the economic grid, it is apparent that countries or population groups having a Situation Index value in the range of 2.5 or below, are characterized by features of the zone of subsis-

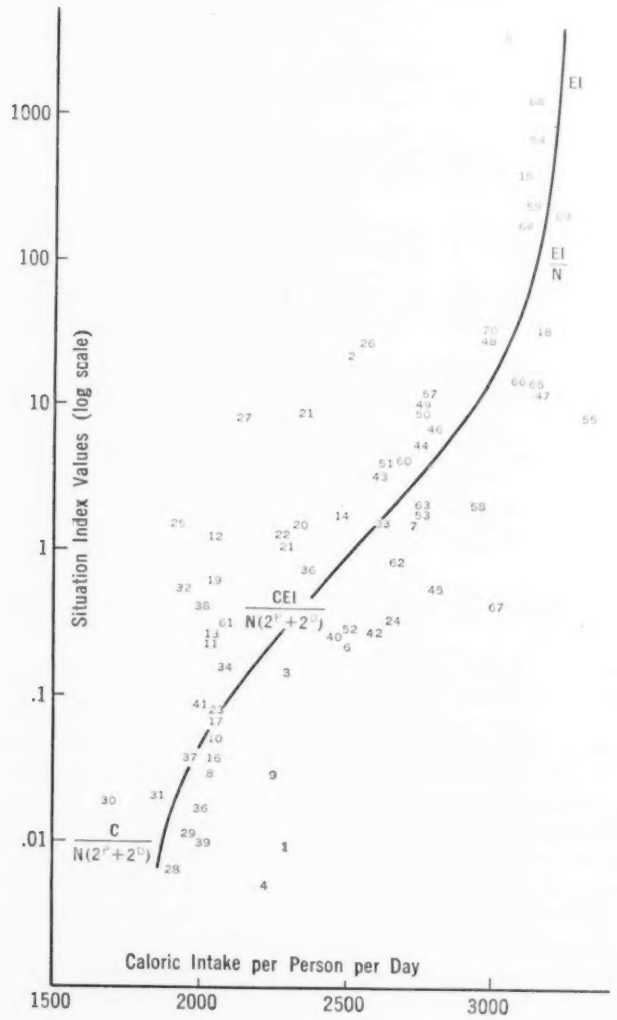

Fig. 7.—Situation Index values in relation to caloric intake, different countries and territories (see Legend, Fig. 3, for identification).

tence. From the information laid down, indications are that the daily intake per person must be approximately 2700, that per capita annual income must be in the range of $300, and that the industrial energy consumed per year per person must be about 1.4 tons coal equivalent, before the country or population group can be said to exist in a category which benefits from the accelerating improvement process made possible by savings and investment which in turn make possible industrial development.

Further understanding is obtained by referring to the health and nutritional grid and by considering impediments to progress (Fig. 8). In Stage 1 of the bioeconomic pathway, human effort is devoted primarily to the aquisition of food and to reproduction. For population groups barely above the threshold of subsistence, increasing availability of food, as we have seen, may easily result in greater fecundity, thus neutralizing or preventing any generalized improvement. While overall food production may be caused to increase, per capita intake may remain stationary or even decrease. Countries in this situation are caught up in what may be called a *subsistence spiral,* in which case food production and population size expand together and no improvement in level of living occurs. The diameter of such a spiral, it might be said, is determined by the limits of natural food materials (game, fish, crop products), and its duration by the ability of the people to regulate fertility (if such is possible among underprivileged peoples) thereby permitting the opportunity to pass from Stage 1 over into Stages 2 and 3. Education, which under other circumstances lays a foundation for technical and industral development, in Stage 1 is largely wasted due to low life expectancy.

Recent changes in India may be taken as an interesting example of food and fecundity relationships. During 1934–1938, India (according to reported figures) had an average daily caloric intake of 1940 and a birth rate of 3.1% per year, while in 1946–1950 the caloric intake was 1700 and the birth rate 2.5%. The difference between birth rate 3.1 and 2.5% in India at the present time represents more than 2 million people yearly. Although birth rate is affected by numerous factors other than nutrition, indications are that birth rates follow caloric intake rather closely at this level of food consumption. Accordingly, it is to be expected that as nutrition rises again to 2000 calories or slightly more, there will be a significant increase in number of births each year. Whether such an increase will result in actual population increase will of course depend on accompanying death rates.

Above Stage 1 is Stage 2, which is characterized by maximum birth rates followed by a tendency toward decline. In situations where caloric intake is in the range of 1700 to 1800 per person per day and population density is high, the problem with respect to bioeconomic improvement is somehow to hurdle Stage 2, thereby getting over into Stage 3 where cultural development tends to hold fecundity in check. But in Stage 3 another spiral is encountered, one turning in the opposite direction, so to speak. While cultural development may act during the latter part of Stage 2 and during Stage 3 to reduce birth rates, it acts at the same time to bring down death rates, in some instances to an extent that net population gains may be larger than before. Above the *high fertility hurdle,* then, is the *health improvement spiral,* the diameter of which might also be regarded as measured by the limits of resources and its duration in terms of abilities and determination of the

people to industrialize. Stages 1, 2 and 3, which, in combination, correspond with the zone of subsistence, may therefore be visualized as consisting of human effort directed toward bio-economic improvement, and a natural force, mainly in terms of numbers of people making demands for materials, acting to direct the course downward rather than upward.

In the change from Stage 3 to Stage 4, with productivity becoming greater than unity, there are opportunities for the improvement process to be accelerated. But Stage 4 also has problems. For the most part, these are problems of choices. Productivity above amounts required for full health and a moderately satisfying cultural life results in products which can be consumed as luxury items rather than used to provide more lasting benefits. Taking *luxury consumption* as one of the choices of Stage 4, there are two others. One is to have more offspring, in which case there is a third spiral: a *luxury growth spiral,* as it were; which, depending on the availability of resources and the opportunity to industrialize further, may hold progress in check. The other is investment in education, research, machines, insurance, social security and other means by which capital can be caused to multiply and cultural gains to expand. People who comprise the populations characterized by Stage 4, due to the educational and technical opportunities which they have, are able to know the difference between frugality and wasteful living, also to know the consequences of overfertility and to reduce it if they wish. For them it is largely a matter of decision whether they will advance into Stage 5, which is identified almost entirely by opportunities for accelerating cultural gains.

At the right in Fig. 8 are names of countries, which, according to Situation Index values, exist at one or another of the stages indicated. Implications are that dominant features of each stage characterize the countries that fall at the different levels, and, in general, this appears to be true. The Asiatic countries shown in the Stage 1 category have increased productivity significantly during recent years, but there is question as to whether level of living has advanced, due to the possibility that productivity has not kept pace with population growth. Certain of the Latin American countries, as grouped in Stage 2, obviously are riding the crest of the high fertility wave, a behavior which could continue so long as there is land area for expansion. The countries of Stage 3 are clearly transitional; a considerable degree of cultural advancement has been achieved but a high level of living is lacking as yet. Stage 4 contains the countries of Western Europe, particularly those that have benefited from colonization. Agricultural and industrial developments and also conditions of health are advanced, but all have high concentrations of people. Whether the higher levels of living can continue or be advanced still further will be determined largely by the balance maintained between population and industrial growth. Countries of Stage 5 are far enough advanced and with sufficient resource reserves, to afford luxuries and at the same time benefit from the factors of acceleration. Because of the retarding features of Stages 1, 2 and 3, and of the accelerating features of Stage 4, and particularly Stage 5, the general trend is toward a widening gap between the high and low level countries so far as level of living is concerned.

Not all countries,however, are characterized precisely by one or another of the categories alone, either by the grid system of Fig. 1 or the transition pattern of Fig. 6. This, in part, is the

meaning of the spread of points in Figs. 2 through 5. Some countries are more advanced in certain respects and less advanced in others. Virtue of the Situation Index approach is that countries can be located generally in the pattern of development and then analyzed for the relative strength of component determinants of level of living. Recent conditions in Japan will illustrate. According to the Situation Index, Japan falls in Stage 2. However, according to its advanced industrial development (0.9 ton coal equivalent consumption per year per person), it should be in Stage 3; but, by considering other components, it is found that Japan's population increase rate is high, that population density is also high, and that caloric intake and income are low. These factors act together to offset the industrial advantage and place Japan in Stage 2. The component analysis procedure described in Paper II is useful in developing an understanding of conditions in specific countries.

Actually, the deviant countries are in some ways more interesting than those that fit closely to what appears to be the "natural" or "more normal" pattern of development. Moreover, study of deviants in itself gives considerable insight into the mechanism of advancement and into particular problems with which specific countries are confronted. In Fig. 2, post-war birth rates are found to be more scattered than those for pre-war. Explanation might be expected in terms of disruptions caused by the war, but indications in Fig. 3 suggest otherwise. In Fig. 3, it is seen that despite the ravages of war which ordinarily result in higher death rates due to malnutrition and spread of disease, death rates actually fell generally. Since health programs were introduced widely throughout the world, both during and after the war, it is likely that

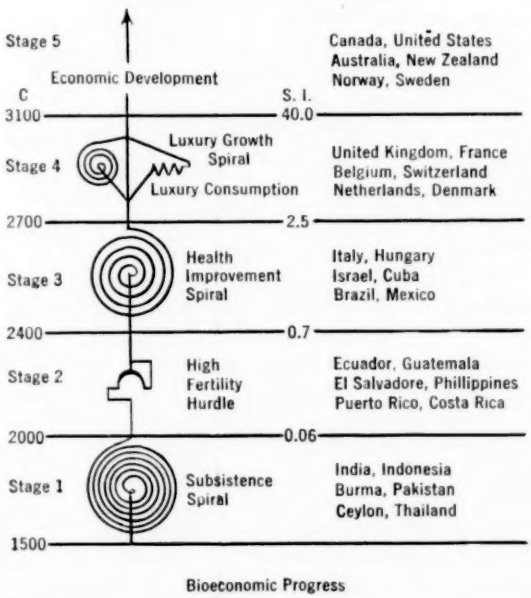

Fig. 8.—Bioeconomic progress showing impediments.

these were responsible for the death rate decline and that they influenced birth rates in somewhat irregular fashion at the same time.

Figure 3 shows two other points of particular interest. The first is greater prevalence of low death rates among countries with low caloric intake, and the second is difference in level of the pre-war and post-war death rate curves. Assuming that health programs may have been to a large degree responsible for both, it is apparent that some countries are being catapulted forward in their development with respect to death rates, without other "usual" developments going along concurrently. The difference in level of the stable portions of the two curves is about 0.2%. Should this be at all representative for the entire world, it would appear that the number of lives being saved each year by newer health measures is something more than 5 million. It is significant that some of the most effective public health techniques are largely exogenic; that is, applied to population groups without particular effort on the part of the people themselves (for example, DDT for the control of insect-borne diseases), and without the cultural development which may bring down birth rates. Where low death rates are superimposed on high birth rates (countries with 1900 to 2300 caloric intake), it will be of interest to see whether the populations involved can avoid being thrown downward into the low birth rate subsistence spiral of Stage 1.

THE SITUATION INDEX FORMULA AS A MODEL. The background thus developed lays a foundation for more complete explanation of the Situation Index formula as a model characterizing the entire process of bioeconomic development.

This formula, $\frac{CEI}{N(2^P + 2^D)}$, is based squarely on the idea of *supply and demand*. In essence, it implies that level of living varies inversely with the number of people making demands for the materials which are available. Since availability of materials to each person determines level of living, the ratio of per capita productivity to fertility gives an index of level of living. In basic elements, then, the formula is an expression for per capita productivity divided by an expression for total fertility, $\frac{CEI}{2^P + 2^D}$, where (P) is population increase rate and (D) is death rate. Since the limits of resources are also matters of concern, and since these bear some relationship to land area, particularly in the case of more agricultural countries, an expression for population pressure is regarded as more significant than one for fertility alone, thus giving the basis for the full formula.

In the early phase of bioeconomic development, that is, Stages 1 and 2, as we have identified them, the process is influenced most strongly by agricultural and food gathering features in terms of calories per person as the numerator, and fertility in relation to land area as the denominator, $\frac{C}{N(2^P + 2^D)}$. In the middle phase, Stages 3 and 4, industrial and economic features, as well as agricultural, contribute to productivity, and fertility as a feature in population pressure continues to be an important influence, thus necessitating use of the full formula in this range. In Stage 5, agricultural productivity above the level of 3100 calories per person, as emphasized, has meaning almost entirely in economic terms, and fertility as determined by birth and death rates tends to become fixed at a lower level. Thus, by dividing caloric intake by 1000, as we have done for use in the formula, the factors for caloric intake

and fertility tend to cancel out when development is in the Stage 5 range, leaving in effect a numerator consisting of economic and industrial factors and a denominator of population density, $\frac{EI}{N}$. In late phases of bioeconomic advancement, where level of living is dependent much more on industrial development than on land productivity, the density factor becomes less important and less significant in the reaction, though not entirely inconsequential. In late phases, therefore, the improvement process is characterized mainly by the expression (EI) only. The positional applicability of these expressions is shown both in Fig. 1 and Fig. 7. Since $\frac{C}{N(2^P + 2^D)}$ covers adequately the early part of the reaction which is mainly biological, and since (EI) covers adequately the late part which is mainly economic and industrial, the full formula covers adequately throughout the entire range.

The bioeconomic reaction, it is believed, can be characterized usefully in terms of six components, as implied by the formula. The influence of each component is indicated depending on whether it is added, multiplied or used as a power, and the magnitude of effect is determined by the choice of units used in connection with each component.

Income, as emphasized repeatedly, is in itself a reasonably satisfactory over-all measure of productivity, taking account as it does of the ability and skills of the people as well as the availability of resources. Its range of influence is expressed fairly conveniently in monetary units, which vary among different countries, in United States 1950 dollars, from less than 50 to nearly 1500. Income figures alone, however, make no provision for acceleration, which as we have seen is necessary in characterizing the reaction correctly. To bring in this feature, income has been multiplied by values for food intake which exert their strongest influence during early development, and by industrial energy consumed which exerts its strongest effect in the later phases. Since the quantitative value of units which are multiplied makes no difference so far as sequential index relationships are concerned, we have found it convenient, and, we believe correctly meaningful, to use caloric intake (divided by 1000) and tons coal equivalent as units respectively. Inasmuch as the range of caloric influence is from about 1500 to 3100, the quantity of 1500 (or 1.5) logically should have been deducted; however, for the purpose of obtaining a more favorable balance between caloric intake and fertility, it was considered more appropriate that this value be retained.

The range of influence resulting from energy consumption expressed in tons coal equivalent is from about 0.02 to more than 8.0. When the figure is less than 1.0 a depressing effect is exerted, causing the productivity figure to be reduced, and when it is above 1.0 a positive effect is exerted. The depressing effect is regarded as necessary inasmuch as an agricultural economy without some industrialization represents a very low level development. Similarly, the positive influence is regarded as necessary to define properly the compounding effect of savings and investment. In brief, then, the numerator of the over-all expression is composed of income values modified by multipliers which exert their respective influences more strongly at different levels, and both of which contribute to acceleration, negative or positive depending on quantitative values with respect to unity.

The denominator, as characterized fairly completely in Paper I, is comprised of two components, population density and total fertility, which are multiplied to give the accelerating influence of population pressure. The first, in terms of inhabitants per square kilometer, varies from 1 to more than 600, and the second from about 3 to 25 in abstract units representative of the geometric progression characteristic of the compounding growth process. Using per cent natural population increase (P) and natural population decrease (D), death rate, as powers of 2 and then added together, gives a total fertility factor characteristic of the growth process. The denominator, therefore, consists of a strong density factor accelerated by fertility which changes geometrically. That the factor for land area should exert a strong effect in the early phase of development, we believe, is as it should be, since early development is more agricultural and since the extent of agriculture is related to land area.

With more experience and with the availability of more accurate basic data, it may be possible to choose units somewhat more suitably and to arrange the relationships of component determinants somewhat more precisely. The main problem to this point has been to develop a picture of the operating mechanism, leaving ultimate preciseness for later handling.

Summary. 1. Based on information about biological and economic processes, improvement in level of living has been recognized as a mechanism operating under the influence of various component determinants, some of which assume a dominant or pacesetting role at one stage and others at another stage.

2. Utilizing nutrition as a measure of progress, birth and death rates, life expectancy, and infant mortality were analyzed in such a way as to reveal turning points and stages that have particular meaning.

3. On the basis of turning points, and also knowledge of biological and economic processes, three graphic representations of progress were developed: 1) a system of grids (Fig. 1) which shows coexistence of health and economic conditions together with levels of nutrition, energy consumption and income, tending to be associated with different degrees of advancement; 2) a pattern of transitional steps (Fig. 6) which indicates the tendency of countries to move from less stable to more stable conditions of living; and 3) a sequence of impediments that may arise during the course of progress (Fig. 8), depending on the balance maintained between number of people making demands for materials and productivity of the people.

4. By means of Situation Index values, certain countries as examples were located in one or another of the categories defined, thereby making evident the nature of conditions and the kinds of problems likely to apply; examples were also given of countries which cannot be categorized as easily due to accentuated features, and how a procedure of component analysis can be used to identify and reveal the significance of such features along with others.

5. Utilizing the background of information assembled, a fuller explanation was given of the Situation Index formula, as a model, characterizing the entire range of bioeconomic development.

6. Indications are that during the early phase of development, biological factors exert the dominant role, whereas during late phases economic factors assume this role. In the very early phase, nutrition appears to determine conditions of health, which, in turn,

influence or determine reproductive capacity and incentive for cultural development. In the middle range, further improvements in health due to improving nutrition and cultural influence together with cultural development generally, appear to bring about the transition leading to more uniform birth rates in the lower range and to full life expectancy. With the basic requirements for life thus fulfilled, and with per capita productivity becoming greater than "unity" thereby creating the opportunity for country-wide savings and investment, the late phase appears to consist almost entirely of cultural development, which, at this stage, is most significant in terms of economic and industrial progress, involving the feature of acceleration.

7. Based on various types of evidence, the turning point from subsistence to a kind of life with expanding and accelerating social gains appears to be reached when caloric intake per person per day is in the range of 2700, when average annual income is equivalent to about 300 U. S. dollars, and when industrial energy consumption per person per year is approximately 1.4 tons coal equivalent. The figures given are subject to the accuracy of basic data and to the applicability of assumptions made.

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(Previous papers of this series)

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SUMMARIO IN INTERLINGUA

Sanitate Public, Fertilitate, e Economia General in lor Effectos Combinate Super le Standard del Vita

IV. Characterisation de Limines e Stadios Disveloppamental in le Mechanismo Bio-Economic

1. Super le base de informationes relative a processos biologic e economic, nos ha recognoscite que le melioration del standard del vita es un mechanismo que functiona sub le influentia de varie determinante componentes e que certes iste componentes ha un rolo dominante o guidante in certe phases del processo durante que altere componentes ha un tal rolo in altere phases.

2. Utilisante le factor del nutrition como criterio de progresso, nos ha analysate natalitate, mortalitate general e infantil, e probabilitate de superviventia. In le analyse nostre objectivo esseva identificar punctos cardinal e phases de signification special.

3. Super le base de tal punctos cardinal insimul con nostre cognoscentia de processos biologic e economic, nos ha disveloppate tres representationes graphic de progresso. Illos es (a) un systema de rubricas (fig. 1) que monstra le coexistentia de conditiones hygienic e economic con le nivellos de nutrition, consumption de energia, e revenito que tende a associar se con varie grados de progresso;

(b) un assemblage de curvas (fig. 6) exhibiente le passos transitional que indica le tendentia del paises de progreder ab minus stabile a plus stabile conditiones vital; e (c) un schema del consecutive impedimentos (fig. 8) que pote manifestar se in le curso del progresso secundo le grado de equilibrio mantenite inter le numero de personas requirente materiales e le productivitate del population.

4. Per medio de valores ab le "Indice del Stato Presente," certe paises (selegite como exemplos) esseva placiate in le un o le altere del categorias definite. Isto servi a render evidente le natura del conditiones e le probabile typo de problemas associate con illos. Esseva etiam citate exemplos de paises que non es facile a categorisar a causa del presentia de accentuate factores special. Nos ha explicate como un analyse de componentes pote esser usate pro identificar e clarificar le signification de tal factores intra un gruppo de alteres.

5. Utilisante le complexo de datos colligite in nostre studio, nos ha presentate un explication plus complete del formula del "Indice del Stato Presente." Le Indice es representate como un modello que characterisa le integre spectro del disveloppamento bio-economic.

6. Le datos disponibile indica que durante le prime phases del disveloppamento le rolo dominante es illo del factores biologic e que plus tarde ille rolo es capturate per factores economic. In le primissime phase, le factor del nutrition determina apparentemente le conditiones hygienic le quales, de lor parte, influentia o determina le capacitate reproductive e le stimulo del disveloppamento cultural. Al centro del scala, meliorationes hygienic additional (debite al meliorate nutrition e al meliorate influentia cultural insimul con le disveloppamento cultural in general) pare resultar in le transition a un natalitate plus uniforme e a un superviventia probabile maximal. Assi le requirimentos fundamental del vita es satisfacite. Simultaneemente le productivitate per capite excede le unitate de requirimento con le resultato que le pais in su totalitate ha le opportunitate de sparniar e re-investir. Le effecto es que le phases subsequente del disveloppamento pare consister quasi completemente de un disveloppamento cultural. Isto se exprime alora le plus significativemente in progressos economic e industrial e es distinguite per le characteristica del factor de acceleration.

7. A judicar super le base de varie typos de evidentia, le puncto de transition ab subsistentia a un forma de vita con diffusive e accelerative progressos social es apparentemente attingite quando le ingestion caloric per individuo per die es in le vicinitate de 2700, quando le revenito annual median es le equivalente de circa 300 dollars statounitese,-e quando le consumption de energia per anno e capite corresponde a circa 1,4 tonnas de carbon. Iste datos es correcte in tanto que lor bases es correcte, *i.e.* le datos ab le quales illos es derivate e le stipulationes del quales illos depende.

THE EFFECT OF CORTISONE ON THE GROWTH OF ADULT AND EMBRYONIC TISSUES *IN VITRO*°

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In 1952, Nils Carstam[3] presented an extensive review of the literature on the effect of cortisone on tissue culture and isolated cells. Due to the diversity of results[1,2,6,8,9] he found it difficult to draw any general conclusions as to the effect of cortisone in tissue cultures of connective tissue.

The following experiments may help in part to clarify the existing confusion concerning the direct effect of cortisone on cellular growth rate *in vitro*. The effect of cortisone, of sera from cortisone treated dogs, total adrenal cortical extract and ACTH were tested on a variety of standardized strains of adult and embryonic fibroblasts as well as on adult and embryonic epithelium, Gardiner lymphosarcoma, CH_3 mouse breast carcinoma and leukocyte migration. The results show that cortisone inhibits the growth of adult cells much more readily than that of embryonic cells and that embryonic and some other tissue extracts antagonize the growth-inhibiting effect of cortisone *in vitro*[4].

Material and Methods. Fibroblasts were obtained from embryonic chick heart, adult chicken, rabbit and mouse heart, adult mouse diaphragm, and skeletal muscle. Epithelial cultures were obtained from embryonic and adult human skin. Fresh explants, as well as standardized 5th to 8th passage cultures, were used for testing.

Hanging drop cultures of 5th to 8th passage cultures were divided into equal halves, one-half being used as a control and the sister half as the experimental culture. The control and experimental cultures were each cultivated in Carrel flasks containing 0.3 ml. chicken plasma, 0.65 ml. Tyrode's solution plus one drop of dilute chick embryonic extract in order to form a coagulum. After the cultures were allowed to grow for 24 to 48 hours at 37° C. the surface areas were projected and measured according to the method described by Ebeling. The control and test solutions were then added as fluid phase. Tyrode's solution was used as the solvent for ACTH. Cortisone was dissolved in a mixture of equal parts of rabbit serum and Tyrode's solution or in serum only. The same solutions minus cortisone were added to the controls. The cultures were then incubated at 37° C. and the surface areas measured every 24 hours. In some cases the supernatant was decanted and renewed every 24 hours. All culture work was carried out under sterile conditions.

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°°Dr. Andrus was deceased in 1951.

Results. The results obtained with the standardized strains and with fresh explants were essentially the same. However, the results with the standardized strains were more uniform and could be expressed in growth rate curves based on surface area. Each curve represents the mean values obtained from a series of experiments comprising from 50 to 75 cultures for each series.

Cortisone in concentrations from 0.001 mg. per ml. to 0.1 mg. per ml. has a marked inhibitory effect on the growth rate of all adult fibroblasts tested. As will be noted from Fig. 1, cortisone diluted up to 0.01 mg./ml. completely inhibits growth of adult fibroblasts. Also to be seen from Fig. 1 is the fact that cortisone in concentrations as high as 0.1 mg./ml. has no effect

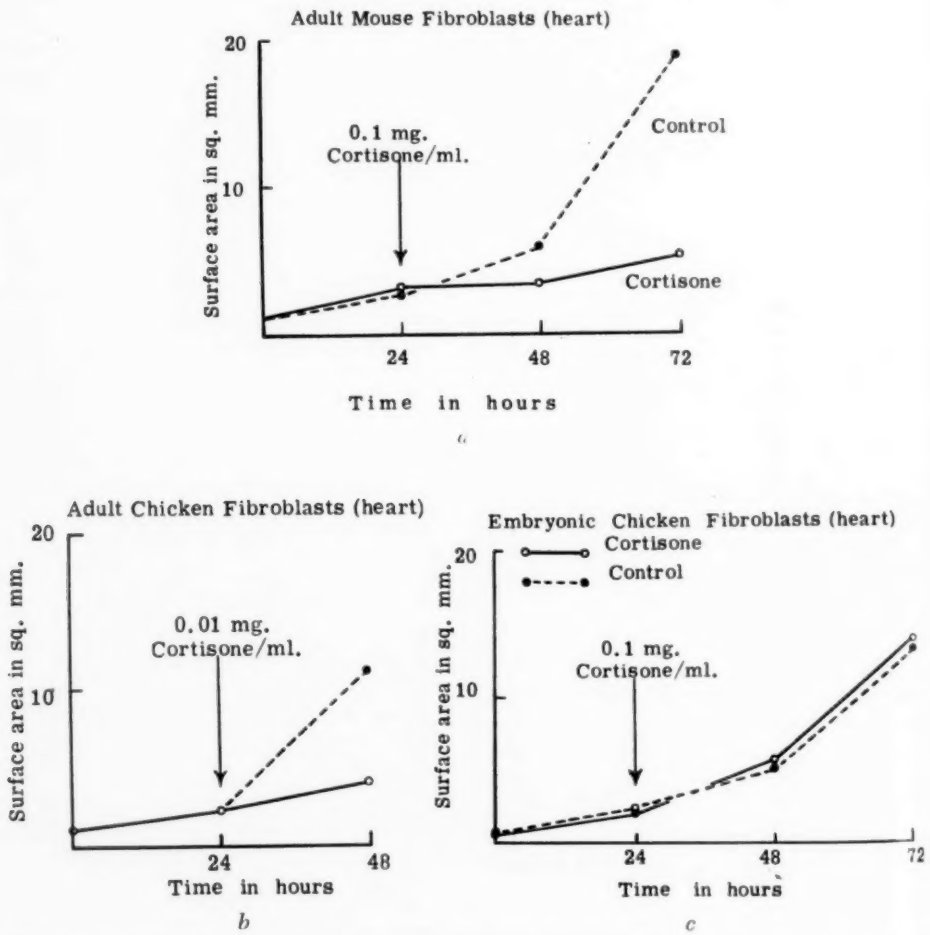

Fig. 1.—*In vitro* inhibition of adult fibroblast growth by cortisone 0.1 mg./ml. *(a)*, and by cortisone, 0.01 mg./ml. *(b)*, contrasted to the absence of effect of the larger amount on embryonic fibroblasts *(c)*.

whatsoever on the growth rate of embryonic fibroblasts *in vitro*.

The inhibitory effect of 0.1 mg./ml. cortisone on the growth of adult fibroblasts is reversible, as may be seen from Fig. 2. Very good growth was obtained after removing cortisone, thoroughly washing the cultures for 48 hours with Tyrode's solution, and then adding 0.5 ml. of 20% embryonic extract.

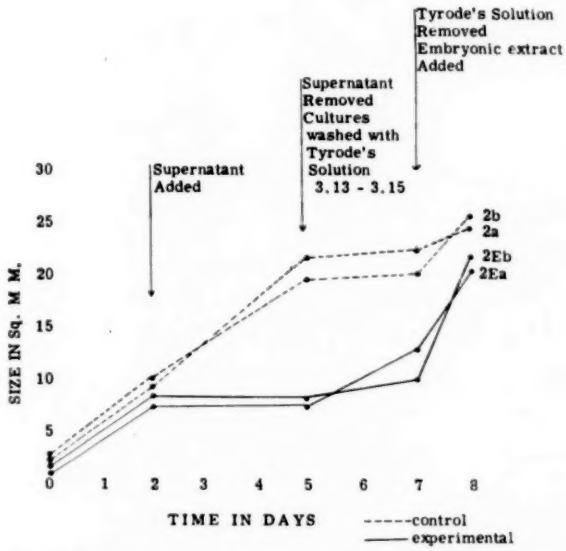

Fig. 2.—Reversibility of growth inhibitory effect of 0.1 mg./ml. cortisone on adult fibroblast.

Figure 3 shows that the addition of embryonic or adult tissue extracts (in this case, extracts of sheep or rabbit cardiac muscle[5] were used), together with cortisone completely neutralized the growth inhibiting effect of cortisone in concentration as high as 0.1 mg./ml. on adult fibroblasts.

Figure 4 shows that neither Gardiner lymphosarcoma nor the CH_3 mouse carcinoma are inhibited by cortisone in concentrations up to 0.1 mg./ml.

EFFECT OF WHOLE ADRENAL CORTEX EXTRACT. In these experiments an Upjohn preparation made up in 10% alcohol containing 2.5 rat units per ml. was used. In preparing control solutions, the amount of alcohol present was taken into account. Figure 5 shows that adrenal cortical extract in concentration as low as 0.025 rat unit/ml. had a marked inhibitory effect on adult chicken fibroblasts growing *in vitro*. Concentrations of 0.0025 unit per ml. had only a slight transitory inhibitory effect for the first 24 hours. However, the growth of embryonic chick fibroblasts is unaffected by adrenal cortical extracts in concentrations as high as 0.25 rat unit per ml.

EFFECT OF CORTISONE *in vitro*. A series of experiments were carried out on the effect of cortisone on migration of leukocytes. Leukocytes from the buffy coat of adult chicken blood were used. A uniform clot of buffy coat was obtained by treating the buffy coat with

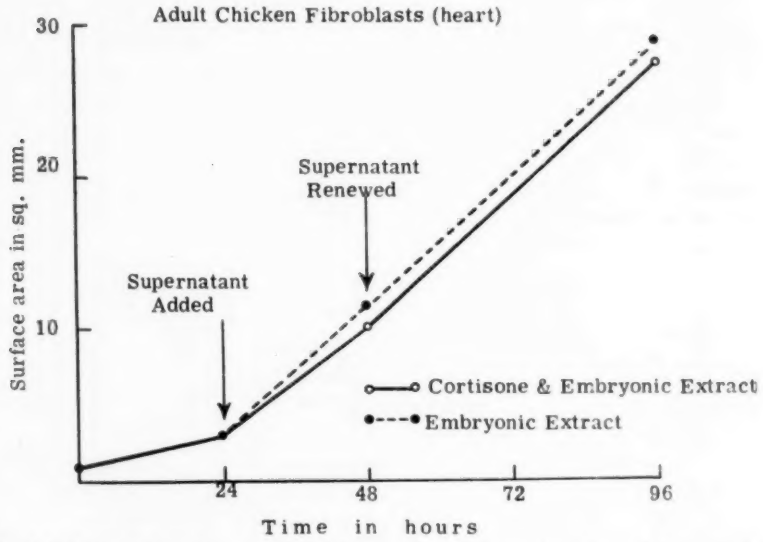

Fig. 3—*(a)* Neutralizing the growth inhibitory effect of cortisone by adult or embryonic tissue extracts.

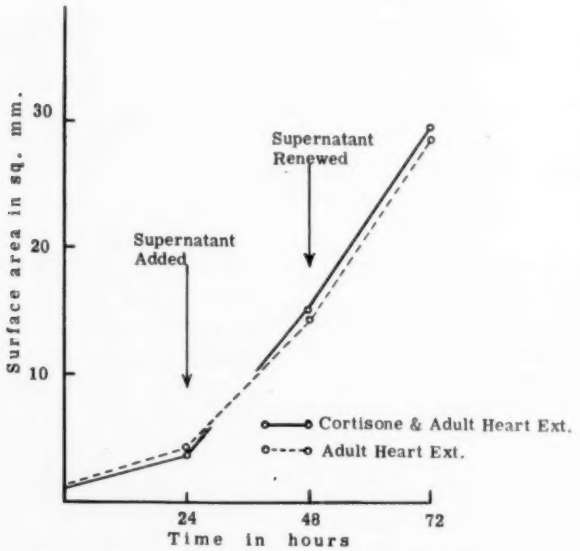

Fig. 3.—*(b)* Neutralizing the growth inhibitory effect of cortisone by adult or embryonic tissue extracts.

one drop of embryonic extract, allowing this to coagulate, then removing the buffy coat layer and thoroughly washing it with Tyrode's solution, thereby removing adherent red cells and extracts. The clot was then cut into small pieces of approximately 1 c.mm. These pieces were planted in Carrel flasks, 5 to 7 pieces in each flask in the same medium as described above for fibroblast cultures. The same technique of projecting and measuring was also employed. Eight flasks were used for each concentration of cortisone and eight flasks as controls. The concentrations studied were 0.1, 0.05, 0.025, and

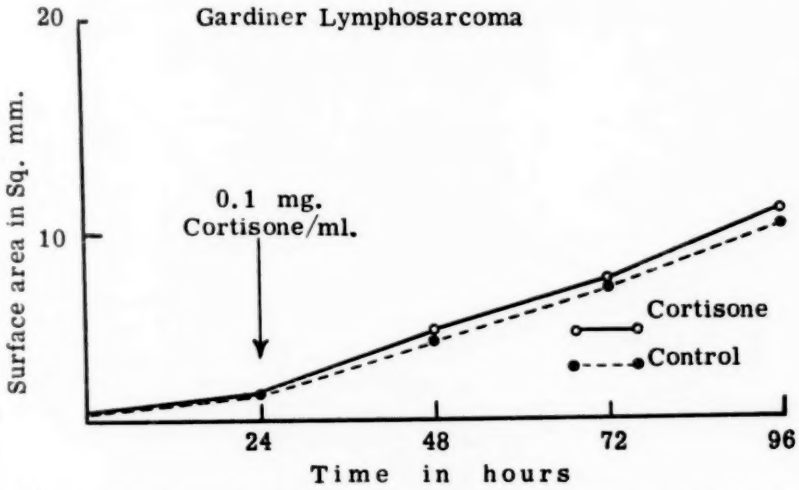

Fig. 4.—*(a)* Absence of growth inhibitory effect of 0.1 mg./ml. cortisone on Gardiner lymphosarcoma or CH_3 mouse carcinoma.

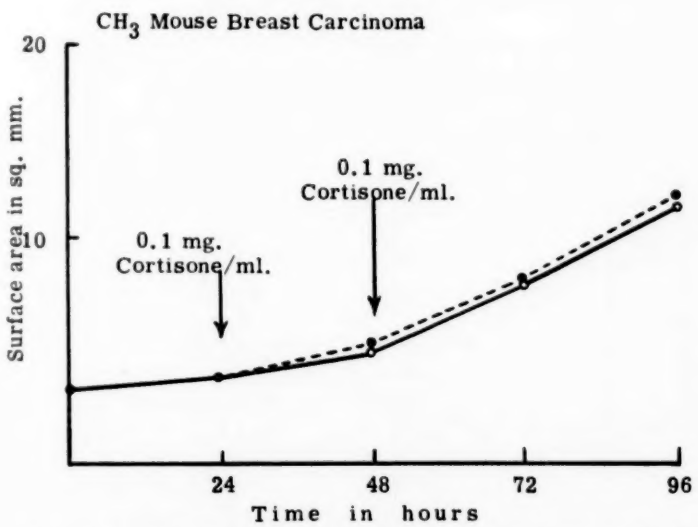

Fig. 4.—*(b)* Absence of growth inhibitory effect of 0.1 mg./ml. cortisone on Gardiner lymphosarcoma or CH_3 mouse carcinoma.

0.01 mg. per ml. of cortisone dissolved in serum. Cortisone in concentrations of 0.1 mg. per ml. and 0.05 mg. per ml. had a marked retarding effect on migration of leukocytes *in vitro*. With 0.025 mg. per ml. there was a lesser effect and with 0.01 mg. per ml. almost no effect (Fig. 6).

EFFECT OF ACTH. ACTH in concentrations up to 0.4 mg./ml. had no effect on the growth rate of adult or embryonic fibroblasts.

EFFECT OF SERA OF CORTISONE-TREATED DOGS ON CELL-GROWTH *in vitro*. Four small healthy adult dogs received daily injections of cortisone of 10 mg. each

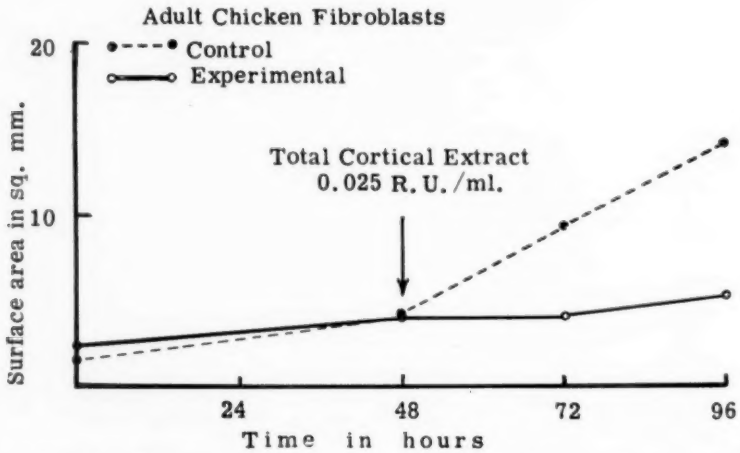

Fig. 5.—*(a)* Growth inhibitory effect of 0.025 rat unit/ml. adrenal cortex extract on adult fibroblasts. Lack of effect on embryonic fibroblasts.

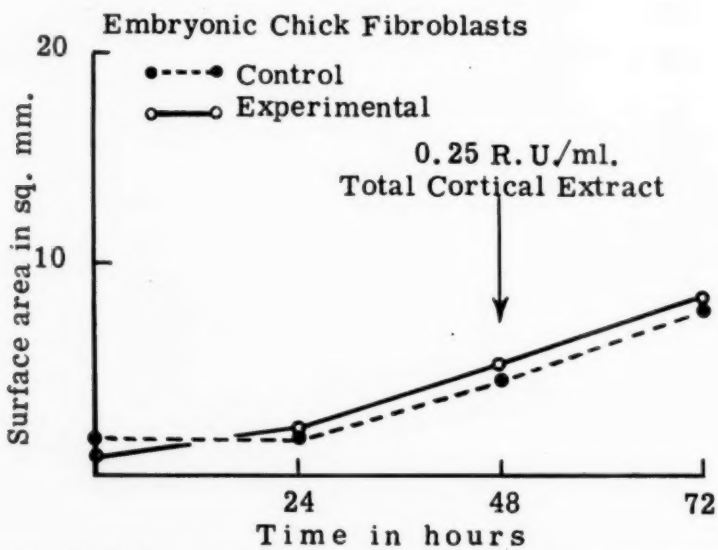

Fig. 5.—*(b)* Growth inhibitory effect of 0.025 rat units/ml. adrenal cortex extract on adult fibroblasts. Lack of effect on embryonic fibroblasts.

with an initial injection of 25 mg. each on the first day. Two dogs were kept as controls and received no cortisone. Under intravenous Nembutal anesthesia symmetrical bilateral squares of full thickness skin, approximately 2 × 2 cm. were excised from the back of each dog. In two dogs cortisone administration was commenced 48 hours before the experimental wounds were made in one case 24 hours prior to and in one case concurrently with excision.

refrigerator for 24 hours, then centrifuged at 3500 r.p.m. for 20 minutes and the sera pipetted off. The effects of these sera on the growth of adult fibroblasts *in vitro* were tested individually by adding them as supernatant to 24-hour-old cultures in the same way as described previously. The growth of these cultures was measured every 24 hours. In Fig. 7 the mean size of the cultures 72 hours after the addition of the sera is plotted against the time that

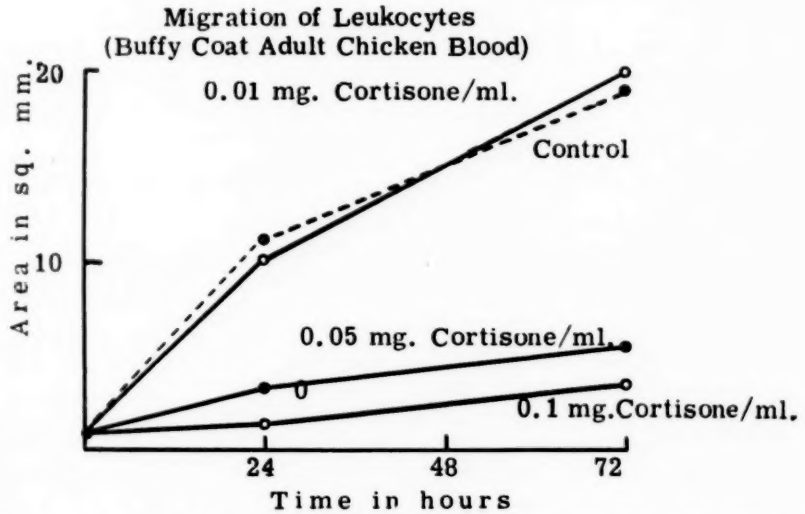

Fig. 6.—Inhibition of migration of leukocytes by 0.1 mg. to 0.05 mg./ml. cortisone.

The wounds were allowed to heal naturally without any treatment or dressings.

All four control wounds commenced granulating after 3 days, whereas the time of onset of granulation in the wounds of the experimental dogs varied from 7 to 9 days. The total healing time was 15 days in the wounds of the untreated dogs, and varied from 20 to 30 days in the cortisone-treated dogs.

Blood samples were taken at stated intervals simultaneously from the controls and from the dogs receiving cortisone. This blood was stored in the

elapsed between the beginning of the daily cortisone treatment of the dogs and the taking of blood. Thus, the abscissa of this figure shows the time during which the dogs received daily cortisone injections and the ordinate indicates the effect of the sera on the growth rate of fibroblasts. The curves show that sera taken from dogs during the first 15 days of cortisone treatment markedly depressed the growth of adult fibroblasts *in vitro*. However, sera of blood taken from the cortisone-treated animals between the 18th to 30th day of daily cortisone treatment showed a

tendency to have less and less of an inhibiting effect on the growth rate of adult fibroblasts. The size of cultures treated with serum taken on the 30th day of daily cortisone treatment is approximately the same for sera from experimental and control animals, showing no inhibitory effect. The disappearance of this inhibiting effect of the sera during prolonged treatment with cortisone points to the appearance of substances in the blood which inhibit or mask this effect of cortisone. It is also of interest to correlate this finding with the one just described: that in cortisone-treated dogs there is an initial retardation of granulation of wounds which is gradually overcome. This finding in a way parallels clinical observations in treatment of rheumatoid arthritis where patients cease to respond to continuous cortisone treatment.

Despite the pronounced inhibitory effect of cortisone on the growth rate of adult fibroblasts growing *in vitro* and the transitory effect in retarding granulation of wounds, it had no noticeable effect on the growth of embryonic chick epithelium or on adult human epithelium *in vitro* in concentrations as high as 0.1 mg. per ml. Epithelization of experimental wounds described above appeared to be entirely normal and unaffected by the continuous administration of cortisone. Ragan *et al.*[11], using rabbits, found that with much higher doses of cortisone (approximately 5 times) granulation was almost completely suppressed, whereas with lower doses corresponding to those used by us and to the human therapeutic dose they obtained merely a delay in granulation time.

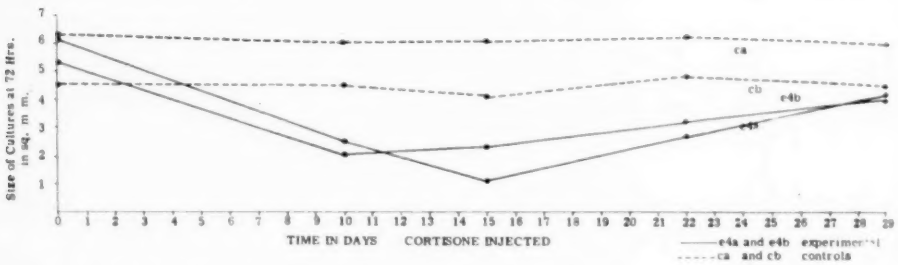

Fig. 7.—*(a)* Sera of dogs receiving daily injections of cortisone (30 days) inhibit growth of adult fibroblasts during the first 15 days. Sera gradually lose growth-inhibitory effect.

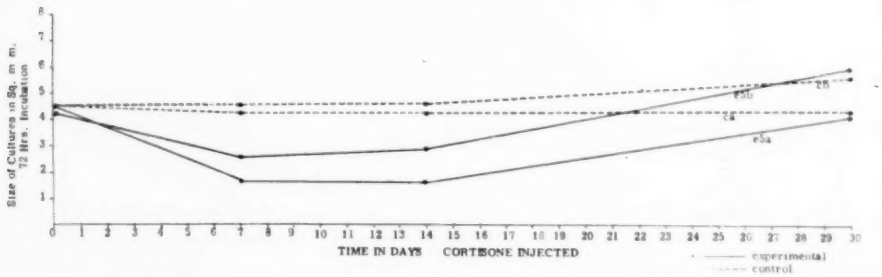

Fig. 7.—*(b)* Sera of dogs receiving daily injections of cortisone (30 days) inhibit growth of adult fibroblasts during the first 15 days. Sera gradually lose growth-inhibitory effect.

Discussion. There are several points in our results which may explain the discrepancies appearing in publications regarding the effect of cortisone on fibroblasts *in vitro*. First of all, the inhibitory action of cortisone in concentrations up to 0.1 mg./ml. is selective for fibroblasts from adult tissue and does not inhibit embryonic fibroblasts. Secondly, the addition of tissue extracts to the media neutralizes the inhibitory effect of cortisone. Embryonic extracts or some other tissue extract in various concentrations are usually a component of culture media.

From work in animals, it has been surmised that cortisone exerts its action on the cellular level. An inhibitory effect on inflammatory response has been shown by Selye[13] and Spain *et al.*[15]. Howes *et al.*[7] found in animals a direct inhibitory effect on the proliferation of fibroblasts as well as on the formation of the fibrils and the ground substance of connective tissue. Spain *et al.*[14] showed a change in ground substance of connective tissue in which hyaluronidase is involved. Our experiments show that cortisone in suitable concentrations suppresses mitosis and migration of adult fibroblasts. Menkin[10] has found that cortisone suppresses the incidence of normal cleavage of fertilized Arbacia ova *in vitro*.

Our experiments were all short-term tests. The further question being pursued at present is whether exposure for prolonged periods, such as several weeks, of adult fibroblast strains to cortisone *in vitro* will result in any ability of the adult fibroblasts to overcome the inhibitory action of cortisone on their growth.

Summary. 1. The effect of cortisone, of ACTH, and of sera of cortisone-treated dogs has been tested *in vitro* on the growth rate of adult and embryonic fibroblasts.

2. In concentrations of 0.1 to 0.01 mg./ml., cortisone had a marked inhibitory effect on the growth rate of adult chicken, rabbit and mouse fibroblasts.

3. Cortisone in the above concentrations had no inhibitory effect whatsoever on the growth rate of embryonic fibroblasts.

4. The inhibitory effect of cortisone on adult fibroblasts was reversible.

5. The addition of embryonic or adult tissue extracts together with cortisone to adult fibroblast cells growing *in vitro* nullifies the growth inhibitory effect which cortisone in concentrations of 0.001 mg./ml. to 0.1 mg./ml. normally has on adult fibroblasts.

6. Addition of 0.1 mg./ml. cortisone to the culture medium of cells of a mixed tumor (originally a spontaneous mammary adenocarcinoma of a CH_3 mouse) results in cultures consisting primarily of carcinoma-like cells. The cells of the control cultures without cortisone were primarily sarcoma-like. Cortisone in this concentration, however, did not inhibit the growth of this CH_3 mouse tumor. Addition of 0.1 mg./ml. cortisone did not inhibit the growth of cultures of the Gardiner mouse lymphosarcoma.

7. Whole adrenal cortical extract (Upjohn) also inhibited the growth of adult fibroblasts.

8. ACTH in concentrations up to 0.4 mg./ml. had no effect on the growth rate of adult or embryonic fibroblasts.

9. Cortisone in concentrations up to 0.05 mg./ml. had a marked retarding effect on the migration of leukocytes *in vitro*.

10. Sera of blood taken from dogs during the first 15 days of cortisone treatment markedly depressed the growth of adult fibroblasts. Sera of blood taken from dogs between the 15th and 30th day of daily cortisone

treatment showed a progressive reduction in their growth inhibitory effect which disappeared completely by the 30th day.

11. Cortisone in concentration of 0.1 mg./ml. had no retarding effect on growth of adult human epithelium or embryonic chick epithelium *in vitro*.

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(Interlingua on page 450)

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A METHOD FOR PREPARING THAWED ERYTHROCYTE-GLYCEROL MIXTURES FOR TRANSFUSION*†

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Human erythrocytes have been successfully stored in a medium containing glycerol at temperatures below freezing for several months[11]. After 9 months storage at —79° C., erythrocytes which have been freed of glycerol by dialysis[7,12] have shown a post-transfusion survival which compares favorably with that of the erythrocytes in freshly drawn blood[8]. The removal of glycerol from thawed erythrocyte-glycerol mixtures by dialysis is a slow and cumbersome procedure. Washing procedures[2,6] for rapidly removing glycerol from such mixtures are not satisfactory because of the severe sludging which occurs. To make this low temperature method of storage practical for routine use, there is need for a simple method of converting a thawed erythrocyte-glycerol mixture to a suspension of erythrocytes which is ready for transfusion.

An erythrocyte-glycerol mixture cannot be transfused directly because the osmotic forces would cause rapid lysis of the cells. The human erythrocyte is very permeable to glycerol and so the erythrocytes in an erythrocyte-glycerol mixture are markedly hypertonic because of the glycerol they contain. If these hypertonic cells were injected into the circulation, the isotonic environment would cause the hypertonic cells to imbibe water rapidly, swell and rupture. If this osmotic swelling and rupture of the cells could be prevented, it should be possible to transfuse these erythrocyte-glycerol mixtures without the necessity of completely removing the glycerol. The present investigation has been directed to this problem and the method set forth below has been developed which permits the transfusion of thawed erythrocyte-glycerol mixtures after storage at low temperatures.

The method developed is based on the fact that the human erythrocyte is much less permeable to glucose than to glycerol. Thus if a glucose solution of appropriate concentration is added to a thawed erythrocyte-glycerol mixture, the glucose does not penetrate the cells appreciably, and it provides an osmotic pressure outside the cells which approximately balances the osmotic pressure due to the glycerol which is inside the cells. After the addition of glucose the mixture is diluted with a relatively large volume of isotonic saline with no more than slight hemolysis occurring. The resulting relatively dilute suspension of erythrocytes now has a total osmotic pressure which is low enough so that very little intravascular hemolysis from osmotic

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†An abstract appeared in Proceedings of the Physiological Society of Philadelphia, Am. J. Med. Sci., **229**, 705, 1955.

forces will occur on transfusion. That this is so has been indicated by *in vitro* experiments which have served (from an osmotic point of view) to simulate a transfusion. Alternatively, this dilute suspension of erythrocytes can be centrifuged once and resuspended to provide a high hematocrit product, the total osmotic pressure of which is very nearly isotonic.

Materials and Methods. Packed erythrocytes, obtained by removing most of the plasma from blood collected in acid-citrate-dextrose (ACD) anticoagulant, are mixed with an equal volume of a solution which contains 40 gm. of glycerol, 2.5 gm. of sodium citrate and 0.2 gm. of citric acid per 100 ml. After equilibrating for about 30 minutes at 5° C., such mixtures were then stored at −20° C. for periods up to 6 months. Thawing of the mixture is accomplished by immersing the bottle in a large 40° C. water bath and mixing the thawing contents until no ice remains. To the thawed mixture is added concentrated glucose solution (50 gm. glucose and 0.9 gm. sodium chloride per 100 ml.) in the proportion of 50 ml. of glucose solution per 100 ml. of thawed mixture. After standing 10 minutes at room temperature, the mixture is quickly diluted with twice its volume of 0.9% sodium chloride solution. This resulting suspension of erythrocytes now contains approximately 4.5% glycerol and 5.5% glucose in addition to the electrolyte and has a total osmotic pressure which is about 4 times that of blood plasma. Simulated transfusions, as described below, have been carried out on portions of this low hematocrit suspension. In some experiments this latter product was centrifuged, the supernatant liquid removed and the cells resuspended in saline or plasma to give a suspension with a hematocrit of about 50%. Simulated transfusions were also carried out on these high hematocrit suspensions.

The simulated transfusion is done in plasma (150 ml. in a conical flask) which is maintained at 37° C. and is kept in vigorous motion by means of a magnetic stirring apparatus. The suspension of erythrocytes (50 ml.) is run into the plasma at the rate of 25 drops per minute through an ordinary intravenous needle the point of which is situated just above the surface of the plasma. The use of a larger volume of plasma relative to the volume of cell suspension did not influence the results. A further indication that the plasma volume used is large enough to produce as much hemolysis as will occur from osmotic forces was shown by the absence of hemolysis on washing the cells with isotonic saline after completion of the simulated transfusion. The percentage hemolysis which occurred was calculated from the values for the total hemoglobin content, the hemoglobin content of the supernatant fluid and the hematocrit of a sample.

Results. The results of simulated transfusions of both low and high hematocrit products are shown in Table 1. The total hemolysis figures shown represent all of the hemolysis which occurred in the entire procedure from the initial mixing of the red cells with the glycerol solution until the end of the simulated transfusion. The data of Table 1 show that more than 85% of the original numbers of erythrocytes remained intact after prolonged storage, processing and simulated transfusion.

Discussion. It must be emphasized that the loss of cells being measured in the simulated transfusions is only that which is due to osmotic and other physical forces. These simulated transfusion experiments give no information about the viability of the cells. However, it has already been shown[8] that the erythrocytes in a thawed erythrocyte-glycerol mixture are viable even after prolonged storage at low temperatures. It seems unlikely that the relatively short contact with glucose and saline solutions which the present procedure involves would cause appreciable metabolic deterioration of the cells. It is, therefore, not unreasonable to expect that the cell survivals after actual transfusion might be of the same order of magnitude as those after simulated transfusion. This expectation is being borne out by the initial results of transfusion studies in man which are now in progress.

The proposed method is simple and rapid, can be carried out in a single

closed container and, in its simplest form, requires no centrifuging. This method might make practical the stockpiling of erythrocytes and their rapid processing in a time of emergency when large quantities of erythrocytes might be needed in a short time.

The possible harmful effects or disadvantages of the proposed procedure must be considered. In so far as the recipient is concerned, the transfusion of the high hematocrit product would differ very little from a conventional transfusion of whole blood except that a small quantity of glycerol would be infused. With the low hematocrit product the major differences would be the infusion of a larger quantity of fluid, of a small quantity of free hemoglobin, and of a considerable quantity of glycerol. The infusion of the extra fluid and of a little hemoglobin represents no significant hazard. The effects of the infusion of a considerable quantity of glycerol have not previously been evaluated.

Glycerol is a physiological substance and it is known that it is converted to liver glycogen[3]. Several studies have shown that large quantities can be administered orally to experimental animals and man without adverse effects[4,5]. However, there have been reports[5,9,10,13] of hemoglobinuria, hypotension and convulsions which followed the parenteral administration of glycerol to laboratory animals. A single report[1] of the parenteral administration of small quantities of glycerol in man noted no toxic effects. Accordingly, we carried out a systematic investigation of the effects in the rabbit, the dog and in man of the intravenous administration of glycerol. The toxic effects previously reported have not been observed. These previously reported effects may have been due to the injection of very concentrated solutions of glycerol or of solutions which contained no electrolyte. We feel that it is safe to administer the quantity of glycerol which would accompany the transfusion of 200 ml. of erythrocytes in a low hematocrit product. The amount of glycerol in the high hematocrit product is small and we feel that there is no hazard in the repeated transfusion of this material. The detailed results of our investigation of the intravenous administration of glycerol will be published separately.

Although the results of the *in vitro* experiments reported herein indicate the feasibility of the proposed method for preparing and transfusing thawed erythrocyte-glycerol mixtures, the real usefulness of such a procedure requires the demonstration of successful transfusions in man. An investigation of the post-transfusion survival of the erythrocytes in thawed erythrocyte-glycerol mixtures which have been prepared

TABLE 1.—HEMOLYSIS AFTER STORAGE AND SIMULATION TRANSFUSION

Volume of Red Cells Stored *ml.*	*Time Stored at −20° C.* *days*	*Hematocrit of Transfused Sample*	*Total Hemolysis* *%*
100	1	High	9.3
150	1	Low	9.8
100	6	High	10.7
100	8	High	12.8
200	60	Low	5.2
150	62	Low	3.7
200	180	High	15.6
200	210	Low	5.9

and transfused by the proposed method is now in progress. The results of the initial transfusion experiments indicated that the post-transfusion survival of these erythrocytes is comparable to that of the erythrocytes in conventional blood bank whole blood.

Summary. Erythrocyte-glycerol mixtures which have been thawed after long-time storage at low temperatures cannot be transfused directly because of the osmotic lysis of the hypertonic erythrocytes which would occur. A simple method is presented whereby the osmotic lysis is prevented and the erythrocytes are relatively rapidly prepared for transfusion. The method involves the addition of glucose to the thawed erythrocyte-glycerol mixture to provide an extracellular osmotic pressure to balance that due to intracellular glycerol. A relatively large dilution with isotonic saline is made and this dilute suspension of erythrocytes can be transfused or a more concentrated product can be obtained by a single centrifuging and resuspension operation. The feasibility of the method from an osmotic point of view has been demonstrated by *in vitro* experiments which simulate the osmotic forces which would occur during transfusion.

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SUMMARIO IN INTERLINGUA

Un Methodo pro Preparar Disgelate Mixturas Erythrocyto-Glycerolic al Transfusion

Mixturas de erythrocytos e glycerol, disgelate post prolongate periodos de immagazinage a basse temperaturas, non pote esser transfundite directemente a causa del stato hypertonic del erythrocytos que resultarea in lor lyse osmotic. Es presentate un simple methodo per que le lyse osmotic es prevenite e per que le erythrocytos es preparate al transfusion con relativemente pauc perdita de tempore. Le methodo es basate super le addition de glucosa al disgelate mixtura de erythrocytos e glycerol pro provider un pression osmotic extracellular que balancia le pression osmotic del glycerol intracellular. Es facite un relativemente massive dilution salin isotonic. Iste suspension diluite de erythrocytos pote esser transfundite, o un producto plus concentrate pote esser obtenite per un sol processo de centrifugation e resuspension. Le practicabilitate del methodo ab le puncto de vista osmotic esseva demonstrate per experimentos in vitor simulante le fortias osmotic que occurrerea durante le transfusion.

PROGRESS
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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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LABYRINTHINE (VESTIBULAR) FUNCTION TESTS
II. INTERPRETATION

BY A. HARRY NEFFSON, M.D.

IN a previous paper[19] a review of the techniques used in performing the various vestibular function tests was given, together with a description of the anatomy and physiology upon which these tests are based. It was pointed out that since so many of these tests need to be done in the doctor's office, it is essential that a test be used which is both simple to perform and yet adequately informative. Such a test would seem to be one of the many modifications of the Kobrak caloric test. The individual examiner should choose one of these methods and use the same technique in all his patients, so that the results can be comparable. Since there are many sources of error in these tests, it is essential that there be as few variations as possible. An accurate record should be kept, both of the method used and the results obtained in each case. In those cases where it is desirable to secure more detailed and quantitative information, one of the more elaborate and complicated tests, as described in the aforementioned paper[19], can be performed, the particular one depending upon its availability.

In addition to the vestibular function tests a complete hearing examination should be made, including tuning fork, audiometric, spoken and whispered voice tests, and tests for recruitment, as a further help in making a correct diagnosis.

It should be remembered that, unless a test result is so strikingly positive as to leave no doubt whatsoever in the examiner's mind, conclusions should not be based upon a single examination. When the tests are definitely positive or definitely negative, they are of great value in ascertaining the degree of viability of a labyrinth, in differentiating between a peripheral and a central lesion and between an infratentorial and a supratentorial lesion, and in helping to diagnose a cerebellopontine angle tumor.

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It must be borne in mind that these tests are not infallible. They have their limitations because of a lack of complete knowledge of the neuroanatomic pathways, the fact that the vestibular responses represent various stages of progress for each condition and the responses change with the progression of an intracranial lesion, and because of occasional errors on the part of the examiner in making his observations and interpreting the results, particularly in atypical cases. In some instances the tests are of great value, particularly early in the disease before neurologic signs are well developed. In those cases, by the time a diagnosis can be made by neurologic methods, it may be too late for complete surgical extirpation. It should be noted that they can aid in the localization of a lesion, but not in the determination of the *nature* of the lesion. The tests are also of help in making an early diagnosis of actual or imminent intracranial invasion in cases of acute or chronic middle ear suppuration and cholesteatoma. They serve as an important tool in otologic, neurologic and neurosurgical diagnosis.

SPONTANEOUS MANIFESTATIONS AND THEIR SIGNIFICANCE. Before proceeding with the various stimulation tests for vestibular function a check should be made for the presence of any spontaneous manifestations of disturbed vestibular function. These include the presence of spontaneous nystagmus, positional or postural nystagmus, spontaneous past pointing, spontaneous vertigo, and the tendency toward falling.

SPONTANEOUS NYSTAGMUS. One of the most significant single findings is the presence of spontaneous nystagmus, especially that which occurs with the patient's eyes looking straight ahead.

Spontaneous nystagmus is a frequent finding in patients with intracranial lesions. In a study of 673 cases of brain tumor, Nylén[20] found spontaneous nystagmus in 57%. Maybaum and Grossman[17] stated that in 13 of their 15 cases of pontine angle tumor spontaneous nystagmus was present, but its direction was of no value as an indication as to the side of the lesion. Santamarina[25] found spontaneous nystagmus in 12 out of 30 patients with intracranial lesions. It was present in 6 out of his 10 patients with verified infratentorial tumors and in 6 out of the 7 patients with tumors of the acoustic nerve, but there was no spontaneous nystagmus in his 13 patients with proved supratentorial lesions.

Spontaneous nystagmus which is vertical or oblique is usually indicative of disease of the central nervous system. According to Fischer and Wolfson[11] vertical nystagmus is pathognomonic of a central lesion due to pressure on the vestibular nuclei in the brain stem by a neoplasm, cerebellar abscess, trauma, and so on. Spontaneous vertical nystagmus appearing in the presence of an abscess of the temporosphenoid lobe indicates that the abscess has ruptured into the ventricular system. Nystagmus which is in a different direction in the two eyes is always due to a central lesion.

POSITIONAL OR POSTURAL NYSTAGMUS. This is a type of spontaneous nystagmus which appears when the head is held in a particular position. Also, it is often associated with vertigo when the head is placed in that position. Dix and Hallpike[7] think it is due to a disturbance in reciprocal reaction between otoliths in the utricle and sensory elements in the canals. Nylén[21] believes that the disturbance may be limited to the perilymph and endolymph, which produce nystagmus by direct action on the labyrinthine membranes or sensory organs, and they cite in substantiation a case of positional nystagmus following fenestration.

It is important to ascertain the presence of this type of nystagmus, because it is a sign of organic disease, either in the central or in the peripheral vestibular apparatus. Although the significance of the various types of positional nystagmus is not completely understood, a good deal of knowledge concerning this condition has been accumulated and consolidated in recent years.

According to Lindsay[16], positional nystagmus of *constant* direction may be found with either central or peripheral vestibular disturbances, but *direction-changing* positional nystagmus is strongly indicative of a central vestibular affection. In most cases of positional nystagmus the central localization of the disorder cannot be proved, since they include intoxications, infections, hyper- and hypo-tension, menopause, vasomotor instability and head trauma. In such patients the caloric response is usually normal.

According to Nylén[21], positional nystagmus can occur in a variety of organic diseases, and inflammatory, toxic, and allergic conditions of the peripheral and central vestibular apparatus. In post-traumatic disorders, the direction-changing type of positional nystagmus may be one of the most common of all neurologic signs.

Cawthorne[5] found positional nystagmus in 127 patients. One group of 13 in which the nystagmus was steady, that is, nonfatigable, included all the patients that had proved or suspected lesions of the central vestibular apparatus. In 114 patients, the positional nystagmus was paroxysmal or fatigable and was considered to be of the peripheral type. In most of the group with central lesions the nystagmus appeared in more than one position of the head, and the direction of the eye movements either changed or remained unchanged with a change of the head position. In the peripheral group the nystagmus was usually seen only with the head in one position, nearly always with the affected labyrinth undermost. Vertigo is usually slight in the central group, more severe in the peripheral group. The caloric test was abnormal in 31% of the peripheral group, and in 62% of the central cases. Remissions often occur in the positional nystagmus of the peripheral type and it is often self-limiting.

Aubry, Pialoux and Bouchet[1] classify positional nystagmus into four types: 1) spontaneous nystagmus in which the direction is modified by certain positions; 2) spontaneous nystagmus which is intensified by certain head positions; 3) no spontaneous nystagmus except in certain positions and 4) nystagmus which appears when the patient is in a dorsal decubitus position, with the head hanging. Based upon 128 proved lesions of the central nervous system, the authors state that types 1, 2, and 3 were found mainly with subtentorial lesions, and type 4 was found in supratentorial lesions. When the positional nystagmus is of peripheral origin it is mainly of type 3, sometimes type 2. Vertigo is constantly present and is always intense. With a sudden change of position the vertigo is increased; in positional nystagmus of central origin the vertigo is unaffected by changes in head position. In positional nystagmus of peripheral origin vertigo and nystagmus tend to subside or disappear with repeated changes of head position, and the nystagmus is nearly always horizontal rotatory.

SPONTANEOUS VERTIGO. In intracranial lesions this vertigo is either slight, transient or absent altogether. When there is substantial rotational vertigo, it is nearly always due to peripheral, labyrinthine disease, rather than to a central lesion.

FALLING TENDENCY. If the patient is able to stand, a Romberg test should

be performed. In patients with intracranial disease, this test is often positive. Santamarina[25] stated that the pelvic girdle test, or attempt to overthrow, was often positive in patients with intracranial lesions, especially in those with infratentorial and cerebellopontile angle tumors.

SPONTANEOUS PAST POINTING. Spontaneous past pointing was present in 5 out of 18 cases of cerebellopontine angle tumor reported by Maybaum and Grossman[17], but the direction of the past pointing was of no help in localizing the lesion. In Santamarina's[25] cases spontaneous past pointing was found more often in patients with cerebellopontine angle tumors. When it was present and could not be modified by vestibular stimulation, an organic cerebellar lesion was suspected.

According to Tschiassny[27], in *peripheral* lesions the slow component of the nystagmus, the past pointing, and the falling tendency are directed toward the side of the lesion, whereas the sense of vertigo is toward the opposite side. The nystagmus is horizontal and rotatory. The direction of falling changes when the position of the head is changed, in line with the direction of the slow component of the nystagmus. Usually these symptoms disappear after a few weeks. In *central* lesions (of the pons or medulla) the nystagmus can appear in any plane, the slow component being directed toward the good side, but the falling is directed toward the side of the lesion, independent of the position of the head and in the same direction as the quick component of the nystagmus. Past pointing is in the direction opposite to that of the sense of vertigo. In cerebellar lesions there is spontaneous past pointing with only one arm.

In summary, the findings of the various workers would indicate that:

A. *In Peripheral Lesions.* 1) The *spontaneous* nystagmus is of the mixed type, horizontal rotatory; it is of short duration and is accompanied by labyrinthine and cochlear disturbances. 2) The *postural* nystagmus is often paroxysmal, fatigable, and always in the same direction, no matter what the position of the body or head. It is usually seen only with the head in one position, with the affected labyrinth undermost. Remissions occur often. 3) The spontaneous vertigo is strong and is increased with a change of position. It is associated with impaired hearing and tinnitus. 4) The spontaneous past pointing is in the direction of the slow component of the nystagmus. 5) The falling tendency (Romberg test) is in the same direction as that of the slow component of the nystagmus and this direction changes with changes of the head position. 6) The slow component of the nystagmus, the past pointing and the falling tendency are directed toward the side of the lesion. 7) All these symptoms usually diappear after a few weeks.

B. *In Central Lesions.* 1) The *spontaneous* nystagmus is of the pure type; it can be in any plane, may be in different directions in each eye, is of long duration, and is often accompanied by neurologic signs. Its direction is of no value as an indication as to the side of the lesion. It is usually absent in supratentorial lesions. Good hearing may be present. 2) The *postural* nystagmus is nonfatigable, may be of constant direction or changing direction, and appears with more than one position of the head. 3) Spontaneous vertigo is usually slight and is unaffected by changes in the head position. 4) Past pointing is often present in posterior fossa lesions, but the direction is of no help in localizing the lesion. 5) The falling tendency is often present. Its direction is toward the side of the lesion and is unchanged with a change in the head position. The pelvic

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girdle test is often positive in patients with infratentorial lesions.

Interpretation of Abnormal Responses to Vestibular Stimulation. Abnormal vestibular responses can occur from disease conditions involving the labyrinth itself, the vestibular nerves, the vestibular centers, or the central pathways. (For a more detailed description see Part I of this paper[19], under "Neural Pathways.") Generally speaking, absent or diminished responses may be due to peripheral disease, but perverted responses are of central origin.

RESPONSES IN PERIPHERAL LESIONS. In a patient with a peripheral lesion *all* the responses are impaired, thus, the presence of any *one* normal response to stimulation suggests a normal labyrinth and a normal peripheral portion of the eighth nerve.

RESPONSES IN CENTRAL LESIONS. Of the utmost importance is the early discovery of a central lesion. Following vestibular stimulation a central lesion should be suspected 1) when there is a perverted, inverted, dissociated or mixed nystagmus, or when the nystagmus is accompanied by conjugate deviation of the eyes or nystagmoid movements; 2) when normal responses are obtained from the canals in one plane and there are abnormal or absent responses from the canals of the other plane; 3) when there is definite and persistent spontaneous past pointing which is not altered by the vestibular stimulation; and 4) when nystagmus is produced, but vertigo or past pointing or both, are absent, or *vice* versa.

LOCATION OF CENTRAL LESIONS. When the presence of a central lesion is suspected, an attempt should be made to locate it. Based upon our present knowledge of vestibular responses, intracranial lesions can be subdivided into three main groups: supratentorial, infratentorial, and cerebellopontine angle.

SUPRATENTORIAL LESIONS. (Cerebrum, its tracts and appendages, including the medial and lateral geniculate bodies.) In patients with these lesions the vestibular responses are often difficult to evaluate. In addition to the spontaneous findings pointing to involvement of the central nervous system, there may be 1) an impairment of the vestibular responses from one ear with good hearing on that side and impaired responses from the vertical canal of the opposite ear, and 2) good resistance to the pelvic girdle test. In general there is increased sensitivity to the vestibular stimulation.

According to Santamarina[25], if a supratentorial lesion is suspected and there are impaired responses when testing the vertical canals of one side, the lesion is more likely to be on the opposite side. If the impaired responses are obtained when testing the horizontal canal of one side, the lesion is more apt to be on the same side. In cases of lesions of the pituitary gland the vertigo is usually of shorter duration than the nystagmus, and other signs of central nervous system involvement are present on testing for spontaneous responses and after vestibular stimulation. With lesions of the suprasellar region the vertigo is much less prominent than the nystagmus, and there are impaired responses on testing the vertical canals of one side; also, there is poor resistance to the pelvic girdle test. In cases of occipital lobe lesions there may be a loss of responses to vestibular stimulation, perverted responses from the horizontal canals, and prolonged and increased past pointing out of proportion to the vertigo.

INFRATENTORIAL LESIONS. (Medulla, pons and cerebellum.) Maybaum and Grossman[17] from a study of 40 verified cases stated that the characteristic findings on caloric stimulation in a patient with a lesion of the posterior fossa with localization in the cerebellum are:

1) diminution or absence of vertigo and past pointing (or past pointing in the wrong direction) and 2) normal nystagmus, unless pressure on the brain stem causes deviations from the normal, such as spontaneous vertical or oblique nystagmus, or perverted nystagmus on stimulation. The hearing is normal. However, occasionally pressure on the eighth nerve by a cerebellar neoplasm may cause hearing impairment of a nerve type. Spontaneous past pointing in one direction or absence of past pointing following vestibular stimulation is suggestive of a cerebellar lesion. On the other hand, when there is normal past pointing with each hand it is probable that the cerebellum is normal.

Santamarina's[25] findings can be summarized as follows: 1) Vertigo is often found to be markedly diminished, almost never increased, after vestibular stimulation. 2) Since there is ipsilateral cerebellar muscle control, abnormal vestibular responses on one side suggest a lesion on that side. If the responses are abnormal on both sides, the lesion is likely to be near the midline. 3) There are disturbances of equilibrium and co-ordination such as inability to perform the finger to nose test and adiadokokinesis. 4) The pelvic girdle test is often positive, that is, there is poor resistance to attempts to overthrow the patient with an infratentorial or cerebellopontine angle tumor (also Shuster[26]). On the other hand, in supratentorial lesions there is a high degree of resistance. 5) Hearing is normal, except when the lesion in the posterior cranial fossa is secondary to a labyrinthitis or is located in the cerebellopontine angle.

According to Brunner[3], *bilateral* caloric stimulation produces a positive reaction in a patient with an infratentorial tumor, whereas there is no reaction in the case of a supratentorial tumor. Fischer and Wolfson[11] also stated that bilateral calorization produces nystagmus in patients with a posterior fossa lesion, but not in anterior fossa lesions.

CEREBELLOPONTINE ANGLE LESIONS. In these cases the vestibular examination is of the utmost importance for early diagnosis, before the appearance of advanced neurological symptoms which indicate extensive involvement and portend difficult surgical extirpation. A tumor in this situation can destroy the eighth nerve and produce a typical picture of a *peripheral* lesion on that side and, in addition, cause pressure phenomena which manifest themselves by the various signs of a *central* lesion on testing the opposite canals.

In addition to the presence of spontaneous findings indicating involvement of the central nervous system, the diagnosis is based upon 1) a diminution or absence of vestibular responses on one side, 2) impairment or loss of hearing, especially for the high tones, on the same side, and 3) impaired responses from the vertical canals of the opposite side. The lesion is on the same side on which the cochlear and vestibular responses are impaired. Occasionally, there are perverted or diminished responses from the horizontal canal of the opposite side. In general there is diminished sensitivity to the vestibular stimulation.

Maybaum and Grossman[17] stated that the most common symptom in their group of 18 verified cases was the loss of hearing. In 16 of these 18 cases there was a total loss; in the other two, hearing was markedly or moderately impaired. The neoplasm was found on the side corresponding to the loss of hearing. In the earlier stages the finding of tinnitus and partial hearing impairment of the nerve type, with vertigo, often leads to a diagnosis of Ménière's disease. As the loss

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of vestibular function develops, the diagnosis becomes apparent.

It should be cautioned that there may be variations from this characteristic reaction, making the interpretation far more difficult. For example, the patient's hearing on the unaffected side may be impaired due to a previous suppurative process in the middle ear or a degenerative process of the eighth nerve. Also, stimulation of the horizontal canal on the unaffected side may cause an equivocal response making it difficult to decide whether or not to consider it the response of a normal canal. In cases of this type other tests indicate a central lesion. In one of the cases cited by Maybaum and Grossman[17], vertical nystagmus resulted from stimulation of the opposite horizontal canal; in 3 other cases there was wrong past pointing on stimulation of the opposite canals; in 12 of their 18 cases of cerebellopontine angle tumor there was a normal response on stimulation of the opposite vertical canals. They stated that 1) the isolated loss or marked diminution of responses from the vertical canals on the opposite side, 2) the occurrence of perverted nystagmus on stimulation of the opposite horizontal canal and 3) the abnormalities of past pointing, all appeared to be caused by pressure of the tumor on the pons.

ACOUSTIC NEUROFIBROMA. This comprises almost 8% of all brain tumors. It usually begins with tinnitus and hearing impairment. In Revilla's[22] series of 160 proved cases all patients showed both auditory and labyrinthine disturbances. In early cases the hearing impairment may be only moderate, with little loss of acuity for the high tones. Later, pressure causes neural atrophy and produces severe or complete perceptive hearing loss. In Edwards and Paterson's[10] series of 157 proved cases acoustic neurofibroma, vestibular responses were impaired or absent in 98% of the cases; partial or total hearing loss on the side of the tumor was found in 99% of the cases.

The classical description is that vestibular responses are absent on the side of the tumor, with impairment of the vertical canal responses on the opposite side. However, Brown and Love[2], reporting 42 cases, stated that in most cases there was a nonfunctioning labyrinth on the side of the tumor, with normal reactions of both the vertical and horizontal canals of the opposite side.

According to Morris[18], spontaneous nystagmus is present in over 90% of these cases. Characteristically there is a bilateral horizontal nystagmus with the slow movement to the side of the tumor. Caloric stimulation readily reverses the direction of the nystagmus.

There are frequently signs of trigeminal nerve involvement, especially loss of the corneal reflex.

Dix, Hallpike and Hood[8] observed that the loudness recruitment phenomenon was characteristically present in patients with Ménière's disease and absent or incompletely present in patients with acoustic neuroma and cerebellopontine angle tumors. Fowler[14], however, stated that recruitment occurs in "nerve deafness" caused both by lesions of the end organ and by neural degeneration, and offered as evidence an audiogram taken before operation in a case of an acoustic neurofibroma in which recruitment was clearly present. Eby and Williams[9], however, agree with Dix, Hallpike and Hood[8]. They found an absence of recruitment in 8 verified cases of intracranial lesions involving the eighth nerve; in 8 other probable lesions of the eighth nerve, there was little or no recruitment present. In 32 patients with deafness ascribed to Ménière's disease they found loudness recruitment present in every

instance, with over-recruitment in nearly half the cases. Furthermore, when they performed "speech intelligibility" tests, they found that in patients with presumed lesions in the end organ, speech intelligibility reached a maximum, then declined with further increases in intensity (within the intensity range of the audiometer). On the other hand, in 5 out of 6 cases of nerve fiber degeneration, speech became more and more intelligible with increased intensity of sound until the limit of the audiometer range was reached.

Thus, since the loudness recruitment phenomenon is present in patients with lesions in the sensory receptor mechanism (cochlea) and apparently absent in patients with acoustic neurofibroma, this would appear to be a practical test for distinguishing between disease of the end organ and a retrolabyrinthine lesion.

MISCELLANEOUS VESTIBULAR RESPONSES AND INTERPRETATION. Some of Fisher's[12] findings can be summarized as follows:

I. If stimulation of the *horizontal* canal on one side results in 1) normal nystagmus, but no vertigo or past pointing, it suggests a lesion of the inferior cerebellar peduncle on that side; however, if there is 2) no nystagmus, but normal vertigo and past pointing, it suggests a lesion between Deiters' nucleus and the medial longitudinal bundle of that side.

II. If stimulation of the *vertical* canals of one ear results in 1) normal nystagmus, but no vertigo or past pointing, it suggests a lesion of the middle cerebral peduncle; however, if it results in 2) no nystagmus, but normal vertigo and past pointing, it suggests a lesion in the pons, near the medial longitudinal bundle.

III. If stimulation of *all* the canals of one ear results in 1) no nystagmus, vertigo or past pointing, it indicates a lesion of the labyrinth or vestibular nerve of that side; if it results in 2) normal nystagmus, but no vertigo or past pointing, it suggests a lesion of the cerebellar nuclei of that side; if it causes 3) no nystagmus, but normal vertigo and past pointing, it suggests a lesion of the medial longitudinal body of that side.

IV. If stimulation of *all* the canals of *both* ears causes normal nystagmus, but no vertigo or past pointing, it indicates a lesion in the midbrain at the point of decussation of the superior cerebellar peduncles.

Roberts[23], discussing a paper by Coates, Shuster and Slotkin, reported 2 cases in young children, 2 and 10 years of age. In each case there was normal hearing on both sides; the caloric responses from the horizontal canals, on both sides, were normal, but the responses from the vertical canals, on both sides, were absent. In each case the verified diagnosis was a midline lesion, in the vermis.

DIRECTIONAL PREPONDERANCE (See Part I of this paper[19]). This finding may be of considerable importance in the diagnosis of lesions of the vestibular apparatus and its central connections.

Directional preponderance may be present with lesions of the labyrinth, the vestibular nerve, and its central connections. Cawthorne, Fitzgerald, and Hallpike[6] stated that in 20% of cases of unilateral Ménière's disease, directional preponderance was found to the side of the unaffected labyrinth.

Fitzgerald and Hallpike[13] reported that lesions of the temporal lobes were constantly associated with directional preponderance of the caloric responses to the side of the lesion. This finding was confirmed by Carmichael, Dix and Hallpike[4].

Kirstein and Preber[15] studied the relationship between the site of electroencephalographic abnormality and the

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presence of directional preponderance in 67 patients with cerebral disorders. They concluded that directional preponderance in patients with cerebral lesions has no unequivocal localizing value, and the absence of directional preponderance does not exclude a lesion of either the frontal or temporal region. The presence of both directional preponderance to one side and a focal electroencephalographic abnormality on the same side indicates a cortical lesion.

Conclusion. An attempt has been made to present a fairly complete, yet concise, review of the interpretation of vestibular function tests, both the spontaneous manifestations of disturbed vestibular function and the abnormal responses to stimulation. It must be cautioned again that unless a test result is so strikingly positive as to leave no doubt whatsoever in the examiner's mind, conclusions should not be based upon a single examination. These tests can aid in the localization of a lesion, but not in the determination of the nature of the lesion. Properly performed and correctly interpreted, the tests are of great help in distinguishing between a peripheral and a central lesion, and a supratentorial from an infratentorial lesion. They also aid in localizing a lesion of the posterior fossa. They are of unquestionable value in the early diagnosis of acoustic neurofibroma and cerebellopontine angle lesions. Because of our lack of complete knowledge of the neuroanatomic pathways and the varying stages of a tumor's growth during which a test happens to be performed, findings in atypical cases can be confusing. For example, cerebellar neoplasms which have invaded the surface of the cerebellum can cause pressure on the eighth nerve and thus give otologic signs which are interpreted to be those of a cerebellopontine angle tumor. Also, what has been considered a characteristic finding in cases of cerebellopontine angle tumors, namely, absent responses on stimulating the vertical canals on the side opposite the tumor, is frequently lacking.

The tests are also of help in making an early diagnosis of actual or imminent intracranial invasion in cases of suppurative disease and cholesteatoma of the middle ear and they can be of great help in diagnosing the cause of vertigo. They serve as an important link in the chain of otologic, neurologic and neurosurgical diagnosis.

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SUMMARIO IN INTERLINGUA

(See page 427 for original article)

Le Effecto de Cortisona Super le Crescentia in Vitro de Histos Adulte e Embryonic

1. Esseva investigate le effecto que cortisona, ACTH, e seros de canes tractate con cortisona exerce in vitro super le crescentia de fibroblastos adulte e embryonic.

2. In concentrationes de inter 0,1 e 0,01 mg/ml, cortisona habeva un effecto marcatemente inhibitori super le crescentia de adulte fibroblastos de gallinas, conilios, e muses.

3. In le mesme concentrationes, cortisona habeva nulle effecto inhibitori del toto super le crescentia de fibroblastos embryonic.

4. Le effecto inhibitori de cortisona super fibroblastos adulte esseva reversibile.

5. Le addition de histoextractos adulte o embryonic a culturas in vitro de adulte fibroblastos nullifica le effecto inhibitori que le addition de cortisona in concentrationes de inter 0,001 e 0,1 mg/ml exerce normalmente super le crescentia de adulte fibroblastos.

6. Le addition de 0,1 mg/ml de cortisona al medio de cultura de cellulas de un tumor miscite (originalmente un spontanee adenocarcinoma mammari de un muse CH_3) resulta in culturas que consiste primarimente de cellulas carcinomoide. Le cellulas del culturas de controlo (non tractate con cortisona) esseva primarimente sarcomoide. Tamen, in le concentration de 0,1 mg/ml, cortisona non inhibiva le crescentia de ille tumor de un muse CH_3. Le addition de 0,1 mg/ml de cortisona non inhibiva le crescentia de culturas de lymphosarcoma de Gardiner ab muses.

7. Extracto adrenocortical integre (Upjohn) etiam inhibiva le crescentia de fibroblastos adulte.

8. ACTH in concentrationes de usque 0,4 mg/ml habeva nulle effecto super le crescentia de fibroblastos adulte o embryonic.

9. Cortisona in concentrationes de usque 0,05 mg/ml habeva un effecto marcatemente retardatori super le migration de leucocytos in vitro.

10. Seros de sanguine obtenite ab canes durante le prime 15 dies de un curso de cortisona exerceva un effecto marcatemente depressive super le crescentia de fibroblastos adulte. Seros de sanguine obtenite ab canes inter le dece-quinte e trentesime die de un curso de administrationes diurne de cortisona revelava un progressive reduction de lor effecto inhibitori super le crescentia de fibroblastos adulte. Post le trentesime die ille effecto inhibitori dispareva completemente.

11. Cortisona in concentrationes de 0,1 mg/ml habeva nulle effecto retardatori super le crescentia in vitro de adulte epithelio human o de embryonic epithelio de gallinas.

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DERMATOLOGY AND SYPHILOLOGY

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SOME ASPECTS OF PIGMENTATION OF THE SKIN

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CUTANEOUS pigmentation is of great medical importance. At times altered skin color furnishes a specific diagnostic clue. In other instances while pigmentary changes fail to clarify the presenting clinical problem, they provide interesting situations in themselves. In this review we will emphasize significant information available to the clinician dealing with pigmentation or its lack. We will also report in some detail pertinent new and old fundamental discoveries on the pigment problem. Since therapy depends on the diagnosis and is still in a state of flux for the purely pigmentary disorders, discussion of treatment will be omitted.

During the course of this review reference will be made to the article by Jeghers[82] who recorded fully the status of this problem as it stood in 1944. The reader's attention is invited to this classic presentation in which useful tables and illustrations are to be found. Other recent surveys include those of Kenny[87] and of Volland[169].

NORMAL CUTANEOUS PIGMENTS. Edwards and Duntley[52] demonstrated by spectrophotometric means that five pigments are present in normal skin. These are carotene, oxyhemoglobin, reduced hemoglobin, melanoid and melanin. They further emphasized the importance of other factors which modified the effects of these pigments. Thus their physical distribution patterns and the thickness and optical properties of the tissue overlying them influenced the

final color produced. Light entering a colorless turbid medium overlying a pigment undergoes scattering which favors a predominance of blue color. Light which is not scattered (by a less turbid medium) contributes more red coloration. Sheard and Brunsting[28,141] performed earlier experiments analyzing skin color by spectrophotometric methods.

Carotene, precursor to Vitamin A, is a yellow compound which strongly influences skin color. It is stored in the subcutaneous fat and also in the stratum corneum where lipid substances abound. This accounts for the yellowish hue of the palms and soles which possess a thick stratum corneum. The white appearance of the conjunctiva and the lack of yellow pigmentation of the tongue are understandable, since both lack a well developed stratum corneum.

Oxyhemoglobin imparts a red color to the skin but its effect is blunted by the presence of melanin which prevents its visibility. Thus it is difficult to recognize erythema in deeply pigmented Negro skin.

Reduced hemoglobin contributes a bluish hue to the skin and is most prominent in conditions productive of true cyanosis.

Melanoid is a substance of poorly understood nature which has a specific absorption band. It is present in amounts paralleling those of melanin and is, therefore, considered to be a melanin derivative. It gives a brownish color to the skin.

Melanin is the term used to denote the brown pigments which originate as oxidative polymers of tyrosine or orthodihydroxyphenyl compounds. These pigments are found throughout nature and are useful in camouflage and in protecting the individual from harmful radiations[133,158]. Since this is the most important of the cutaneous pigments, chief attention will be paid to it.

Racial Variations in Skin Color. As far as is definitely known at present, racial variations in skin color depend upon quantitative differences rather than qualitative ones. Thus the greater pigmentation of the Negro and Oriental races is primarily the result of an increase in melanin and melanoid. Gates and Zimmerman[70] added strength to this view by finding that macroscopically determined skin color depends on the amount of melanin in the epidermis and especially in the stratum germinitivum and spinosum. The small amounts of melanin within melanophores of the dermis do not influence skin color of colored races. Kikkawa *et al.*[89], however, have recently demonstrated a qualitative difference in the amounts of various metals present in hairs of blondes, brunettes, Mongoloid peoples and Negro races. In general they found that the darker the color, the more copper and iron was present. As a result of these and other determinations using insects, animal and human material, they suggested that a certain qualitative "relationship existed between coloration and the type of metal found." This was true especially in pigments assumed to be derived from tyrosine; namely, white is associated with nickel, yellow with titanium and red with molybdenum, blackish color involving blue, green and brown is associated with copper, cobalt and iron. Qualitative pigmentary differences have been found among various strains in lower mammals, that is, mouse and guinea pig[65,72]. The term "redskin," applied to the American Indian tribes, refers to their use of red pigments for ceremonial purposes.

Niedelman[115] has reviewed abnormalities of pigmentation in the Negro. No attempt will be made here to present the subject thoroughly. However, several factors must be taken into ac-

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count when interpreting dermatologic disturbances in general or pigmentary disorders in particular in Negro patients. First of all, deeply pigmented skin often reacts to trauma or inflammation by either a marked increase or decrease in pigmentation. Thus it can be seen that many bizarre patterns of abnormal pigmentation in the Negro skin can be explained on a relatively simple basis. Secondly, pigmented skin makes the detection of erythema or other discoloration difficult. Thirdly, pigmentation of the skin is said to afford some protection from irradiation. Negro skin was said by Fox[66] to suffer less frequently and less severely from skin diseases than white skin. Fox added the following generalizations: 1) Mulattoes are more susceptible to skin diseases than are full blooded Negroes, 2) Negroes are less susceptible to skin irritants than are whites, 3) Negroes are more susceptible to new growths of connective tissue origin and less so to neoplasms of epithelial structures.

Lowenthal, cited by Niedelman[115], indicated that lax areas of Negro skin are likely to be darker in hue, while taut-stretched areas are usually of lighter color. These facts depend upon the decrease in concentration of melanin when the skin is stretched and the opposite effect when it is loose.

Futcher[68] found a sudden transition in the degree of pigmentation on the anterior deltoid regions of the arms of some Negroes. The flexor aspect was less deeply pigmented than the adjacent outer surface, thus forming a sharp line of demarcation. Approximately 13% of 200 individuals examined exhibited this variation bilaterally.

NORMAL PRODUCTION OF MELANIN. Our knowledge of the processes by which melanin formation takes place has advanced steadily since Bloch[22] discovered the DOPA reaction. He immersed pigmented human skin in a solution of dihydroxyphenylalanine (DOPA) and noted that brown granules appeared in the cytoplasm of certain scattered cells of the basal layer of the epidermis. He postulated that this reaction was catalyzed by an enzyme, DOPA oxidase. Controversy as to the existence of this enzyme followed and in 1950 Fitzpatrick *et al.*[60] demonstrated tyrosinase in human skin. They showed that it could initiate the sequence of events necessary to the conversion of tyrosine to melanin via multiple steps of oxidation, molecular rearrangement and polymerization. A potent inhibitor of these oxidative reactions is the sulfhydryl group (SH) found in various compounds in the skin.

Melanin formation takes place in special cells (melanocytes, clear or dendritic cells) in the basal layer of the epidermis. Most investigators believe that these cells originate in the embryonal neural crest and migrate to the basal layer[51,53,109]. The pigment may then be injected into neighboring cells (cytocrinia) or it may remain within the distended dendritic processes of the melanocyte forming a cup or sheath about other basal cells[10].

Knowledge of the various normal hormonal influences upon melanin formation have recently been codified and expanded by Lerner *et al.*[99,100]. In addition, Hall and his associates[74] have fully discussed the relation of the adrenal gland to cutaneous pigmentation. Whitlock[176] has discussed the possible role of ACTH in regulating some of the enzyme reactions of melanin production.

Normally the pituitary gland elaborates a substance known as the melanocyte-stimulating hormone (MSH). This hormone promotes melanin formation. Hydrocortisone from the adrenal gland inhibits the release of MSH in a quantitative fashion. Epinephrine and norepinephrine from the adrenal medulla

and adrenergic nerve endings can prevent or reduce the action of MSH on the melanocyte. Serotonin acts similarly. Excretion of noradrenalin is decreased by administration of commercial preparations of ACTH and Compound E (Von Euler cited by Lerner *et al.*[99]). Animal studies suggest that progesterone and estrogens may stimulate the production of melanin by the melanocyte. The role of thyroid hormone is not understood. Lerner *et al.*[100] found that ergotamine, benzodioxane, dibenamine, priscoline and hydergin prevented the inhibition of MSH by epinephrine and noradrenalin. Progesterone and mesatoin darkened frog skin *in vitro*.

TABLE 1.—FACTORS CONTROLLING MELANIN FORMATION[100,133]

	Promote Melanin Formation	*Retard Melanin Formation*
Normal	Oxygen Tyrosinase (Contains Cu^{++}) Dopa oxidase (?) Fe^{++} Vitamin C (early) Ultraviolet light (activates tyrosinase) DOPA Melanophore stimulating hormone[14] Temperature (increased inactivates sulfhydryl groups) Redox potential (when optimal) Progesterone and estrogens (animal studies)	Sulfhydryl groups (SH inhibits tyrosinase) Vitamin C (reducing agent) Compound F (inhibits release of MSH) Adrenalin, noradrenalin and serotonin (can reduce or prevent the action of MSH on the melanocyte) Redox potential (other than optimal)
Abnormal	Ionizing radiation (inhibit SH) Inflammation (inhibit SH) Arsenic (inhibit SH) Increased keratinization (inhibit SH) Topically applied hormones[15] Mesantoin Ergotamine, benzodioxane, priscoline and dibenamine prevent MSH inhibition by epinephrine and norepinephrine	Direct Enzyme Poisons a. Protein inactivators Excessive heat Sulfur dioxide Strong acids and bases Other strong chemicals Antityrosinase antibodies; postulated in vitiligo, and others b. Copper binding agents Hg^{++}—may replace Cu^{++} CO, CN, H_2S, SH containing compounds (thioureas, BAL, Cysteine Competitive inhibitors: of academic interest. All toxic, unite with enzymes. Induction period prolonging factors pH above 7.5 Tween 20, a detergent Increased NaCl concentration. Compounds reacting with melanin Precursors: PABA, not proven *in vitro*. Sulfa compounds Reducing agents Ascorbic acid Hydroquinone and derivatives *in vitro* Unknown Action Hydroquinone and its monobenzyl ether (Agerite Alba) *in vivo* Pentachlorinated naphthalenes, cable insulators

The various factors which accelerate or inhibit melanin formation are summarized in Table 1. Some of them will be mentioned later in the text where

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appropriate. References[15,59,61,98,100,133,174] contain much additional information regarding melanin production.

ABNORMALITIES OF CUTANEOUS PIGMENTATION. Alterations of pigmentation will be considered in a manner governed chiefly by the pigment affected or the color produced. This plan becomes difficult to follow when a combination of pigments in involved.

THE YELLOW PIGMENTATIONS. As has been seen, carotene is normally present in the skin and imparts a yellow hue to it. Abnormally large accumulations of carotene may occur following ingestion of excessive quantities of yellow vegetables (carrots) and fruits (oranges) (carotenemia)[110]. The skin may then assume a markedly yellow color. The color is accentuated in the areas of greatest keratinization (palms and soles) and those with most subcutaneous fat. Spared are the sclerae which contain neither fat nor keratin, the scrotum which has no subcutaneous fat and the mouth which lacks keratin. Carotene may be found in both the blood serum and urine. This lipochrome may be demonstrated in the serum easily by shaking up equal parts of serum, alcohol and petroleum ether and allowing them to settle. Alcohol precipitates the protein, and absorbs the bilirubin. The lipochromes are absorbed by the petroleum ether layer. Normal color returns with reduction of carotene intake.

Large amounts of carotene are also found in *male castrates*, patients with *panhypopituitarism*, *Simmonds' disease* and *hepatic disease*. *Diabetics* are frequently noted to have yellow skin (xanthosis). Even more frequently they have high blood carotene levels. This may be accounted for by increased ingestion of vegetables, poor utilization of Vitamin A precursors and some essential disturbance in lipid metabolism[179].

The yellowish color seen in some patients with *myxedema* is caused by a combination of carotenemia and anemia. Increased melanin deposits may also be found in this affliction. The yellowish cast notable in many patients with uremia is due to accumulation of urochrome[148].

Jaundice is a sign which is well known to all physicians. The color of the skin is variable and has been described as being from faint yellow through deep orange, saffron, yellowish green, green and even bronze or dark brown. It has long been held (perhaps hoped) that the tint present might be of some differential diagnostic value. Thus an orange or saffron color was thought to be suggestive of intrahepatic jaundice, greenish to bronze of obstructive jaundice, green of intrahepatic jaundice with liver damage as well as of receding jaundice[103], and olive green of cholangitis and cholangitic cirrhosis. Bilirubin and xanthorubin are said to cause the orange color and biliverdin in green. A bronze color in jaundiced patients may result from the added factor of increased melanin deposition. Yellowish blue to greenish color produced by the combination of jaundice with cyanosis may be considered a strong indication of tricuspid valve disease[82]. Jaundice persisting for long periods in infancy may result in greenish staining of the deciduous teeth. Persistent discoloration of tissues containing large amounts of elastic tissue (sclerae, blood vessels, cornea, and skin) is accounted for by their bilirubinophilic qualities.

Edematous areas may appear free from icteric discoloration. However, a wheal produced by injection of histamine into nonedematous areas increases capillary permeability for bilirubin so that the wheal becomes yellower than the surrounding skin[94]. A similar effect is noted in the wheal produced by vig-

orously stroking the skin of an icteric patient (yellow dermographism)[46]. A clinical application of these phenomena is found in patients with subclinical jaundice (that is, hepatitis without jaundice). Yellow dermographism may be produced in the absence of clinical icterus, thus aiding diagnosis. Icteric skin is more susceptible to forming the urticarial wheal than is normal skin.

Atabrine pigmentation was seen extensively during World War II in patients treated for malaria. At present one may see it in dermatologic patients treated with the drug, especially those with chronic discoid lupus erythematosus. The pigmentation usually becomes visible within 3 to 10 days after therapy is begun. It is caused by deposition of the drug in the tissues and may persist up to 4 months, though other residua of the disease may persist for years (Schamberg)[135], following discontinuation of ingestion. The discoloration is diffuse, but accentuation occurs on the dorsa of the hands, arms and feet. It may also be more intense in skin folds and circularly around the mouth. The sclerae remain white[136], though this statement has been disputed.

Various *chemicals* used in industry have been found to cause generalized yellowish staining of the skin. Some of them are hepatotoxic, so that jaundice may be superimposed. Dinitrophenol used in the explosive, dye and other industries, as well as for obesity, may stain the skin. Often the sclerae are involved and there may be a yellow tinge to the blood serum so that true jaundice may be closely simulated. Dinitrophenol is rarely hepatotoxic, however. The "tetryl blonde" or "canary" is a striking individual, well known in the explosive industry[140]. A bright yellow staining of the scalp, hands, face and neck occurs which is sometimes followed by an acute dermatitis. Blondes develop a tetryl red color of the hair. The sclerae are not involved and the causative agent tetryl or trinitrophenylmethylnitramine does not affect the liver. Other compounds giving rise to yellow discoloration of exposed parts in industry are picric acid, trinitrotoluene (TNT), styphnate, nitric acid, and hexanitrodiphenylamine. The hair of workers exposed to large amounts of sodium carbonate is bleached yellow[139]. Picric acid in ointment or tablet form has been used for medicinal purposes in the past. In addition to a yellow staining of all body tissues, including sclerae, it was frequently hepatotoxic. A confusing clinical picture was consequently produced.

Additional disorders exhibit both yellowish discoloration plus other more distinguishing features. Thus a patient with *xanthomatosis* may have a chamois or yellow tinted skin. A patient with *systematized amyloidosis* may exhibit a yellow color. Yellowish palms have been noted in *typhoid fever (Filipovitch's sign)* and a brownish yellow to mahogony jaundice has occurred in association with *gas bacillus infections*. The color formed is a sum total of the influences of bilirubin, oxyhemoglobin, hematin and methemoglobin present in the blood plasma. Rarely a yellowish discoloration about the umbilicus results from a *rupture of one of the bile ducts*[144].

MELANIN HYPERPIGMENTATION. As was previously indicated, the major portion of this review will be concerned with the large variety of conditions and factors which may give rise to increased melanin deposition in the skin. Such pigmentary changes may at times provide definitive diagnostic information, but perhaps more often fail to do so because of the lack of specificity of many of the patterns encountered. Yellowish to brown to black discoloration is thus often seen and may be confusing unless

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it is realized that the skin can react to inflammation or injury (mechanical, thermal, chemical, actinic) by producing more melanin and melanoid than is normally present. This probably results from a reduction in sulfhydryl groups[132].

MELANIN PIGMENTARY DISORDERS CHIEFLY OF DERMATOLOGIC INTEREST. Many dermatologic processes have diagnostic features and also present pigmentary disturbances secondarily. Some of these will be discussed here briefly.

Chloasma. The term chloasma refers to various pigmentary changes (invariably caused by melanin) which occur as localized patches or more diffusely over the cutaneous surface. The color may vary from a slight yellowish stain to a deeply pigmented patch. Small lesions about the face are popularly known as liver spots. The etiologic background of this symptom may be diverse. Thus external agents such as pressure or friction, scratching, heat, light, actinotherapy, physiotherapy, application of cosmetics or tars may be causative. Symptomatic chloasma may occur in association with many things including physiological disturbances of the generative organs in women (chloasma uterinum); lymphoblastoma; tuberculosis especially of the retroperitoneal glands; cachetic states; Cushing's syndrome; disturbances of the thyroid gland; adrenal gland tumors; Peutz-Jeghers syndrome; Albright's syndrome; Leschke's syndrome; Rothmund's syndrome, and others. At times an etiologic agent cannot be discovered, in which case the symptom of chloasma is said to be idiopathic.

Acanthosis Nigricans. Acanthosis nigricans is a process of great interest to dermatologists, internists and surgeons which has recently been fully presented by Curth[40,41]. This is a dermatosis in which pigmented verrucous excrescences occur in the axillae and other body folds. The mucous membranes may be involved and multiple nevi or pigmented spots may occur on the skin. Two types are distinguished: benign and malignant. Generally speaking, the benign type appears in childhood, is accentuated at puberty and disappears after adolescence. The lesions are not as pronounced as in the malignant form. Juvenile acanthosis nigricans may be associated with hormonal disturbances such as hypogonadism, Frölich's syndrome and others[143]. Malignant acanthosis nigricans can occur in children, but usually begins in adult life. It may precede or follow the adenocarcinoma which is always associated with it. The cutaneous lesions may improve upon treatment of the highly malignant neoplasm. The prognosis is guarded since patients with malignant acanthosis nigricans usually succumb within 2 years after discovery of the carcinoma. Benign and malignant acanthosis nigricans are often difficult to distinguish. However, if doubt exists after an otherwise negative complete investigation, an exploratory laparotomy is justified[144] to locate the suspected neoplasm which is usually to be found in the gastrointestinal tract, but may be in the generative organs or even in the lung.

Pseudoacanthosis Nigricans. Pseudoacanthosis nigricans is a disorder which resembles true acanthosis nigricans[40]. This occurs in obese, darkly pigmented individuals. The lesions are similar to, though less severe than, those of malignant acanthosis nigricans. Neoplasms are not associated with this eruption and it resolves following weight reduction.

Xeroderma Pigmentosum. Xeroderma pigmentosum is a rare inherited disease which begins in childhood and is characterized by hyperpigmentation, atrophy, telangiestases, and warty malignant growths[118]. In its early stages pigmented lesions resembling freckles appear. Upon further exposure to ultra-

violet light rays, the skin assumes a senile appearance and epitheliomas develop. The tumors are usually basal cell epitheliomas, sometimes squamous cell epitheliomata, sarcomas or even endotheliomas. The clinical picture closely simulates chronic radiodermatitis. Treatment is unsatisfactory and the ultimate prognosis is grave.

Urticaria Pigmentosa. Urticaria pigmentosa is a chronic disease of the skin (sometimes with systemic manifestations, **Berlin, C.:** A.M.A. Arch Dermat., **71,** 703, 1955) beginning early in life and characterized by brownish yellow pigmented macules and nodules[118]. Bullous[7], papular and diffuse telangiectatic types have been described. In 25% of the cases, the disease appears after puberty. The production of an urticarial wheal upon stroking a pigmented lesion is characteristic (Darier's sign). This sign may be absent in affected adults. The cutaneous lesions consist largely of aggregates of mast cells. These cells liberate heparin and histamine, thus producing the wheal. Asboe-Hansen[6] has recently reported this condition in association with bone lesions. He refers to cases reported by other authors in which bone lesions were also found. Biopsy study of the bone lesions was not done, so that actual mast cell tumor involvement of bone is not certain. That urticaria pigmentosa might be a systemic disease was strongly suggested by Ellis's case[54]. This patient died with infiltration of mast cells in the skin as well as in the bone marrow, lymph nodes, thymus and other organs. Even more recently Reilly *et al.*[129] and Berlin[21] have reported cases with equally convincing systemic involvement. The bone marrow, liver and spleen were involved in these latter instances and suggestive lesions of the bone were found by Reilly.

Incontinentia Pigmenti. Incontinentia pigmenti[156] is a disease which may closely resemble urticaria pigmentosa in the infant when bullous lesions are present. Carney[31] states that this is a peculiar skin disease, probably developmental in origin and characterized by an extremely striking and bizarre arrangement of pigmented macules in polyangular flecks, whorls, spidery forms, lines and patches. These chocolate-brown designs do not follow the lines of cleavage or distibutions of nerves nor do they respect the limitations of the mid line. Areas of alopecia may appear on the scalp, and many other ectodermal and mesodermal defects occur. The disease is frequently heralded by inflammatory lesions, especially bullae, in lines and patches. These disappear, recur and finally disappear, giving way to the above picture or an intermediary verrucous stage. Histologically melanin pigment is found to have escaped from the melanocytes in the basal layer of the epidermis.

Two clinical types of this disorder have been described. These are the Sulzberger-Bloch and Naegeli varieties[67]. Asboe-Hansen[7] has described a rare disorder known as bullous keratogenous and pigmentary dermatitis with blood eosinophilia in the newborn female. This may be yet another variant of incontinentia pigmenti. Other recent publications dealing with this rare disease entity are those of Doornink[49], Uebel *et al.*[166], Philpott *et al.*[121], and Cramer *et al.*[37].

Pinta and Syphilis. Pinta[11] and syphilis[153] may cause hyperpigmentation or depigmentation in their later stages. The early lesions of pinta may vary from pink to blue to dark red or purple depending upon the color of the patient's skin, vascularity, and other conditions.

Dermatitis Herpetiformis. Dermatitis herpetiformis, a recalcitrant, pruritic skin disease, characterized by recurrent

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grouped lesions which may be papular, vesicular or bullous, produces hyperpigmentation following resolution of lesions in their areas of special predilection, namely, shoulders, sacrum, extensors of elbows and knees and trochanteric areas.

Vagabondia. Vagabondia occurs in persons of poor hygienic and economic circumstance. The skin is dirty, dry, scaling and crusted. Numerous excoriations are present and hyperpigmentation develops. Such individuals are usually elderly and often infested with body lice. They frequently suffer from malnutrition. It may be that factors of trauma (scratching) and photosensitivity (due to vitamin deficiency) lead to the melanin hyperpigmentation noted. Involvement of the mucous membranes occurs and Addison's disease may be simulated.

DISORDERS OF PARTICULAR INTEREST TO THE INTERNIST. The *various anemias* often exhibit associated pigmentation of the skin. The brownish color of the legs in some anemias is due to deposition of hemosiderin. Hemosiderin may also be more generally deposited in the skin and is thought to stimulate melanin production in some cases[82].

Diffuse melanoderma is sometimes seen in *Hodgkin's disease*. The involvement may be so extensive as to simulate Addison's disease[35,118]. Others of the lymphomas exhibit similar changes but less frequently than Hodgkin's disease[56,82].

The diffuse or more localized pigmentation seen in the *collagen diseases* has been discussed by a number of authors. This sign is prominent in scleroderma[13] and also occurs in dermatomyositis[116] and lupus erythematosus[26,29,86,152]. The stimulus for melanin production in these conditions might be inflammation or adrenal insufficiency.

Whitlock[177] has re-emphasized the occasional association of increased melanin pigmentation of the skin with *hepatic cirrhosis*. From the few cases reported, one might consider such pigmentation to be a poor prognostic sign. The darkening is most pronounced on the exposed surfaces. Whitlock suggests that impaired detoxification of estrogenic substances may account for the phenomenon. This contention may be supported by the fact that administration of estrogens to hypo-ovarian women produces darkening of the linea alba and of already existing pigmented nevi.

The pigmentation common in patients with *sprue* may consist of perioral chloasma[85] or patchy chloasma-like spots diffusely distributed over the body. Some degree of pigmentary change is seen in most cases of sprue[106,162] and seems to improve with treatment of the disease.

Gaucher's disease is an uncommon familial disorder of metabolism in which there is an abnormal storage or retention of large amounts of cerebrosides (kerasin) within the cells of the reticuloendothelial system[128]. The sexes are equally affected and it may occur at any age. Among the signs and symptoms referable to involvement of many organs is pigmentation of the skin which has been considered virtually diagnostic in advanced cases. An uneven, brownish tan pigmentation of the skin, especially the exposed parts, has been noted in approximately 50% of the cases of Gauchers' disease[23]. Mucous membrane involvement does not occur in the absence of infiltration of the adrenal glands by "gaucher cells." Pigmentation may be patchy or in streaks. In extensive cases the skin of the pigmented areas is glossy and scaly and is sometimes ulcerated. This pigmentation extends from just below the knees to a sharply defined margin just below the ankles. It is this latter pigmentation

plus splenomegaly which is believed to be pathognomonic of the disease. A malar flush has been reported in a few cases[73] and the hemorrhagic tendency present as part of the disease may become manifest in the skin. Ocular changes may occur in Gaucher's disease and consist of brownish yellow wedge-shaped thickening or pinguecula of the subconjunctival tissues appearing first on the nasal side of the cornea and then on the temporal side[128].

Gaucher's disease must be distinguished from *Niemann-Pick's disease* and *Tay-Sach's disease*. In the former, infants are stricken and succumb within the first two years of life, their skin is pale, wrinkled and profusely sweating. The subcutaneous fat disappears. The exposed parts and the mucous membranes are diffusely pigmented. There may be patchy involvement of the mouth. As in Gaucher's disease, the increase in melanin is thought to be due to adrenal involvement[122].

Tay-Sach's disease shows cherry-red macular spots and a progressive flaccid paralysis[128].

A reticulated poikilodermatous hyperpigmentation occurs in *Rothmund's Syndrome*[161].

Various pigmentations related to *neurologic disturbances* are reported by Leavitt[96], and are also discussed by Beerman[15]. Some of these will be considered later while others represent post inflammatory change, for example, herpes zoster. Leavitt also mentions peripheral neuritis as a cause for melanin hyperpigmentation in the involved area. Wilcox[180] described a *melanomatosis of the central nervous system* associated with similar involvement of the skin. This was also discussed by Touraine[163]. There may be a pigmented spot on the skin overlying the *spina bifida occulta*. Derbes, Fleming and Becker have discussed *hyperpigmentation of diencephalic origin*[47]. In addition to reviewing hyperpigmentation associated with schizophrenia, encephalitis, ependymoma, hepatolenticular degeneration, Fanconi's disease and others, they report 4 cases of Schilder's disease. This condition (encephalitis periaxialis diffusa) "is a disease of the brain, chiefly seen in children and young people. It is characterized by slowly advancing cerebral blindness and mental deterioration which terminates in complete dementia. There is massive involvement of the white matter of the brain, stopping sharply at the gray matter, so that the cortex and basal ganglia are spared." The hyperpigmentation which occurs simulates that of Addison's disease. The adrenal glands have been atrophic or lacking in some of the reported cases. The authors postulate disordered production of MSH as causing the hyperpigmentation.

Vitamin Deficiencies. The influence of vitamins on melanin pigmentation has been summarized by Rothman[133]. Several vitamin deficiency states are associated with hyperpigmentation of the skin.

Lack of *Vitamin A*, or its excess, occurring for a long time leads to melanin overproduction[34,71,157]. The discoloration of Vitamin A deficiency is largely follicular in location. It has been suggested that the accelerated keratinization process about the follicular orifices in such cases results in depletion of sulfhydryl groups, thereby releasing tyrosinase from its inhibiting effect.

Deficiency of *Vitamin C* leads to hyperpigmentation and its administration sometimes results in partial depigmentation of lesions of chloasma (see table of factors controlling melanin pigmentation). In addition to the direct relationship of the reducing substance Vitamin C to sulfhydryl groups, it may also be that iron deposition in the tissues as a result of the cutaneous bleed-

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ing of scurvy may bind sulfhydryl which inhibits tyrosinase[133].

Pellagra is a light-sensitive deficiency disease in which the lack of the B complex vitamins and tryptophane is incriminated. A pellagragenic factor has been found in corn by Wooley[182]. This substance seems to be a nicotinic acid antagonist. The dermatologic lesions of pellaga are found on the exposed surfaces of the body as well as on the tongue and buccal mucosa. The symmetry of the lesions is striking and characteristic. Extension of lesions often takes place from the exposed to the unexposed parts. Early there is erythema followed in some cases by bullae. If the process is prolonged, hyperpigmentation occurs. In some instances the clearing of the acute dermatitis results in depigmentation of varying degree. The question as to whether porphyrinuria occurs in pellagra is unsettled[118].

Hormonal Dysfunctions. Hormonal dysfunctions are often accompanied by alterations in melanin content of the skin and mucous membranes.

The hyperpigmentation, darkening of old nevi and formation of new ones noted during ACTH therapy (but not cortisone or hydrocortisone therapy) is thought to be due to MSH present as a contaminant.

The hyperpigmentation in *Addison's* disease results from failure of the adrenal gland to produce sufficient compound F to inhibit release of MSH and from its failure to produce adequate quantities of epinephrine and norepinephrine to inhibit the action of MSH on the melanocyte[99,155]. The process is further accelerated on exposed areas by sunlight and in warm areas by heat. The work of Hall *et al.*[74] indicates that melanoid as well as melanin is present in excessive amounts in Addison's disease. Treatment with compound E or F results in diminution of melanin but not of melanoid[74,102]. These authors produced a substance with properties similar to those of melanoid by oxidizing melanin. They also felt that decreased hemoglobin present in the skin accentuated the pigmentation in Addison's disease. The hyperpigmentation following bilateral adrenalectomy for hypertension or malignancy cannot be reversed by administration of compound E.

Clinically, pigmentation may be partial but is usually generalized and diffuse. It is accentuated on the flexures and in body folds as well as on the surfaces exposed to light. The color may vary from bronze to dark or mulatto-like. The mucous membranes of the lips and gums may exhibit dark, grayish-brown patches and there may be disfuse pigmentation of the buccal mucosa. Nevi become darker, sometimes before the generalized pigmentation develops, and new dark nevi appear (black freckles). The skin texture is soft like that of a baby. Whipple's disease (intestinal lipodystrophy)[125] must enter the differential picture as well as many other melanin hyperpigmentations discussed elsewhere in this paper.

Hyperpigmentation during the last trimester of *pregnancy* occurs in areas similar to those affected by Addison's disease. However, the nipples, genitalia and linea alba also become darkened. Darkening of existing nevi occurs and new nevi may appear. Malignant melanomas grow more rapidly during pregnancy. In pregnancy, MSH is released by the pituitary gland despite the increased amounts of compound F simultaneously elaborated. Epinephrine and noradrenalin are present in the usual amounts. It is possible that progesterone and estrogens augment the action of MSH on the melanocyte. It is to be noted that serum copper levels are elevated in Addison's disease and in pregnancy. Lerner and his associates

could not change serum copper levels by administering crude MSH.

Acromegalic hyperpigmentation can probably be accounted for by increased production of MSH by the pituitary gland. The distribution of pigment is well known, being more prominent on the exposed parts. It is more frequently seen in women and is not reported to involve the mucous membranes. There may be diffuse discoloration or small freckle-like macules[82].

Pigmentary changes in *Cushing's syndrome* are inconstant, the purplish striae are usually more prominent than the hyperpigmentation[124]. The tendency of some of these patients to bruise easily and to bleed into their tissues leads to deposition of hemosiderin especially in the skin of the legs. Hemosiderin may in turn stimulate melanin formation as previously mentioned.

Malignant pheochromocytoma of the adrenal medulla produces a different clinical picture from the benign form. Pigmentation simulating Addison's disease may occur and may reflect the poor epinephrine-secreting capacity of the tumor tissue as well as encroachment by the tumor upon cortical cells. Thus MSH is permitted to act upon the melanocytes with less restraint.

Three to seven per cent of patients with *hyperthyroidism* exhibit melanin hyperpigmentation[80]. Jellinek's sign, a marked hyperpigmentation of the eyelids, is occasionally seen in such patients[25]. However, it has frequently been observed that patients with hyperthyroidism may have vitiligo[9]. The mechanisms responsible for this seeming paradox cannot yet be elucidated.

Pigmentations occasionally seen in disorders involving the male and female *sex hormones* are confusing and not altogether constant. Androgens and estrogens given systemically and applied topically tend to stimulate melanin production. This has been found to be true in experimental animals and humans[43,100,133,174].

MELANIN HYPERPIGMENTATION DUE TO DRUGS. With the increased variety of medications used at present, there has been a corresponding rise in the incidence of untoward drug reactions. This subject has been reviewed in this journal by one of us (HB) in 1949[14]. Increased pigmentation may result from many of these by virtue of the presence of inflammation. However, there are several instances in which residual melanin hyperpigmentation is of greater diagnostic importance. *Fixed drug eruptions* provide an example of this. The fixed drug eruption has been defined as a cutaneous disorder with round or oval, seemingly edematous plaques, coin to palm-sized, recurring on various parts of the body and accompanied by itching or burning. The lesions are dusky red at the outset and are sharply demarcated from normal skin. At times bullae develop leaving pigmented patches of varying hue. The recurrent lesions appear at the original sites of involvement. Many of the drugs which have been reported as producing such lesions are listed in Beerman's article[14]. These include phenolphthalein, antipyrine, phenacetin, barbiturates, salicylates, atabrine, gold and arsphenamine.

The occurrence of a diffuse brownish pigmentation during *mesantoin* therapy has been reported by Hunter[79]. He discussed 6 cases in which pigmentation of the face occurred without preceding dermatitis. The color gradually faded when mesantoin was discontinued. The nature of the pigment was not determined. Since Lerner and his co-workers[100] list mesantoin as a substance which darkens frog skin *in vitro*, the hyperpigmentation in Hunter's cases could have been due to melanin.

The yellowish to brown pigmentation

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resulting from ingestion, injection or inhalation of certain *arsenical compounds* is due entirely to melanin and not to the metal itself. Characteristically this melanosis has a "rain drop on a dusty road" appearance due to multiple small nonpigmented areas[160]. The pigmentation usually appears first on the trunk and upper portions of the extremities. Usually the mucous membranes are not involved, but when they are, Addison's disease is closely simulated. Pentavalent and inorganic arsenical compounds are usually responsible for this process. Palmar and plantar hyperkeratoses, arsenical keratoses and peripheral neuritis aid in diagnosis when present. Malignant cutaneous and internal neoplasms may ensue. Arsenic crystals may be demonstrated in the skin by special techniques.

As will be seen later, all of the heavy metal pigmentations may have an added melanin component.

MELANIN PIGMENTATION AND PHOTOSENSITIZATION. *Photosensitization* frequently results in residual melanin pigmentation. It is difficult to say in many cases whether stimulation of melanin production is a postinflammatory phenomenon or is effected by the ultraviolet tanning rays themselves. This subject has been reviewed extensively by Stokes and Beerman[18,151]. Only a few salient aspects of the problem will be discussed here.

It appears that the most important factor in the local reaction of the skin to light irradiation is the ability of various wave lengths to penetrate to certain depths and to excite certain groups of cells in the epidermis and cutis. It has been noted that the various photosensitizing compounds differ in the structures which they select (melanocytes, vessels, endothelium, basal cells, and others). Ultraviolet rays apparently activate the enzyme tyrosinase thereby furthering the oxidation of tyrosine to melanin[98]. The photosensitizing agents enhance the action of the light upon the skin and its components.

Topically applied photosensitizers may lead to dermatitis with subsequent pigmentation. Some of these are encountered in cosmetics, for example, oil of bergamot in perfumes (berlock dermatitis)[57], eosin in lipstick and oil of lavender, vanillin, lime oil, oil of cedar and oil of citron and others, also produce the same effects when applied to the skin. Meadow grass dermatitis and fig dermatitis represent photosensitization effect at least in part[18]. Other such agents encountered in industry have been reviewed[63,140], and some of them are as follows: pitch, acridine, phenanthrene, anthracene, benzpyrine, erythrocin, flourescein and various fabric dyes. Lerner's group[129] states that compounds such as oil of bergamot contain psoralens which increase photosensitivity when applied locally.

Melanoderma due to tars[140] and cutting oils[119] is not infrequently seen. Brownish-yellow pigmentation usually occurs on the exposed parts and may represent photosensitivity effect or postinflammatory change. When due to cutting oils, it is frequently found in the Mediterranean peoples, and may be accompanied by some skin thickening and plugging of follicles. Oils containing chlorinated hydrocarbons are the more frequent offenders. The tar preparations used in dermatological therapy are also incriminated.

Photosensitizers which may be used for medical treatment or tests are as follows: methylene blue, acriflavine, rose bengal, barbiturates, sulfonamides, gold, some arsenicals, chlorophyll, silver, chlorpromazine[90] and phenergan[145]. It is interesting that quinine has been considered a light sensitizer but that atabrine and chloroquin have

been useful in the treatment of chronic discoid lupus erythematosus[88].

Porphyria. Several types of porphyria[84,171,172] may result in cutaneous hyperpigmentation. In congenital porphyria (erythropoietic type of Watson[173]) all patients have photosensitivity and cutaneous lesions. These lesions are often of a destructive nature and appear most prominently on the exposed parts. They are accompanied by a violaceous hue and followed by melanosis. The bullae thus occurring may simulate epidermolysis bullosa of the dystrophic type. Reddish-brown discoloration of the teeth as well as hypertrichosis have also been noted. Type-I uroporphyrins (the most potent photosensitizers among the prophyrins) predominate. Congenital porphyria is probably inherited as a Mendelian recessive and occurs more frequently in males[30,44]. (For complete discussion of porphyrin metabolism in childhood, see Aldrich *et al.*, Am. J. Med. Sci., **230**, 675, 1955.)

Porphyria Cutanea Tarda[27] (included as an hepatic type by Watson) usually begins at middle age or later. The skin lesions are mild but persistent. Low grade blistering and an erosive tendency of the light-exposed skin surfaces with an accompanying violaceous hue and subsequent melanin pigmentation are seen. The discoloration is diffuse or mottled and is sometimes associated with vitiligo of the hands. Sclerodermoid yellowing and hardening of the skin of the face and back of the neck are common. Patients with acute intermittent porphyria rarely show cutaneous signs. However, skin lesions may appear explosively after exposure to the sun in the mixed type (also an hepatic type of Watson). Pigmentation may then follow the earlier erythematous phase. It is necessary to include the mixed type because patients manifesting features of both congenital and acute intermittent porphyria sometimes appear.

TUMORS, NEVI AND RELATED PROCESSES. Various cutaneous tumors may be hyperpigmented due to melanin deposits namely, *basal cell epithelioma, senile and seborrheic keratoses*[12]. The *common freckle* or ephelide occurring on the exposed surfaces of fair individuals, the brownish *lentigo* present on covered areas and the pigmented nevus[17] (ordinary mole) are also mentioned in passing.

Malignant melanoma is a tumor which is not seen with great frequency but is the subject of considerable misconception. Much light has been cast upon this subject by the work of Allen and Spitz[3]. These findings are discussed in the review by Beerman, Lane and Shaffer[17]. Diffuse blue-gray coloring of the skin[112] may occur and large amounts of melanin may be found in the urine. This has been explained by Fitzpatrick, Montgomery and Lerner[62] as being due to the liberation of melanin precursors into the blood stream from the primary or metastatic tumors. These substances become oxidized diffusely throughout the dermis (not in the epidermis). The pigmentation thus produced is blue-gray, not brown, due to its greater depth in the skin with consequent light-scattering[52]. The exposed areas are first affected as would be expected.

There are a number of *syndromes composed of pigmented spots on the skin and other systemic disorders.* Perhaps the best known of these is *neurofibromatosis* in which multiple fibrous tumors are found on the cutaneous surface and at times on the mucous membranes. These tumors are of various sizes and digital pressure sometimes causes them to disappear through a ring in the skin. Hyperpigmented patches of variable size are often scattered over the skin surface. Those

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which are well demarcated and of moderate size are called café au lait spots. These may precede the tumors by several years. Certain cases in which café au lait spots were found without tumors have been considered incomplete forms of neurofibromatosis. Crowe and Schull[38] studied café au lait spots in the general population and in patients with neurofibromatosis. They concluded that:

1. Any person with more than six café au lait spots exceeding 1.5 cm. in broadest diameter is presumed to have neurofibromatosis even in the absence of a positive family history of the disorder.
2. In the absence of a family history a person with five café au lait spots is much more likely to have neurofibromatosis than is a person with one such spot.
3. Persons with less than six café au lait spots and a positive family history are likely to have neurofibromatosis if their pigmented spots are very similar to those of the affected family members.

The *syndrome of Peutz-Jeghers*[120] has become known in the American literature through the reporting of Jeghers and his co-workers[83]. Melanoplakia of the lips and oral mucosa and polyposis of the intestinal tract have been observed to co-exist in a significant number of cases. Melanotic spots on the skin are also reported in such cases. At times the polyps are found to have undergone malignant degeneration. Thus the observation of the skin manifestations and the recognition of their significance becomes highly important. Melanoplakia is a normal finding in some individuals and is also seen in other disease conditions. The differential diagnosis of such lesions is discussed by Troxell[164]. Additional cases have been reported recently by Rankin and Laird[127], and by Freeman and Ravdin (New England J. Med., **253**, 958, 1955).

Polyostotic fibrous dysplasia associated with endocrinopathies and cutaneous melanin pigmentation was reported by Albright *et al.* in 1937[2] and has since been called Albright's syndrome. The brownish blotches simulate those of neurofibromatosis and tend to be located in the regions of bony involvement[1].

Leschke and Ullmann's syndrome[101] consists of the combination of the pigmentary disturbance of neurofibromatosis with retarded growth, mental and somatic infantilism, vegetative endocrine disturbances (pituitary and adrenal) as well as changes in carbohydrate, water and salt metabolism[147].

Fanconi's syndrome[147] which is an unusual combination of disorders including severe refractory macrocytic anemia with pancytopenia, a hypoplastic bone marrow, and a generalized brown melanin-like pigmentation of the skin associated with various congenital defects is another condition seen rarely.

The Mongolian spot and nevus of Ota are considered by Beerman, Lane and Shaffer[17] to be possible variants of the blue nevus. Mongolian spots are patches of bluish-brown pigmentation usually over the sacrum in children of Oriental or Negro parentage. They are present at birth and gradually disappear. The nevus of Ota was described by that author in 1939[81] and is said by Dorsey and Montgomery[50] to be a Mongolian spot of the side of the face and eye. This nevus penetrates deeply into the structures of the face and orbit.

MELANIN HYPOPIGMENTATIONS. The less common melanin depigmentations may result from such diverse circumstances as heredity, drug ingestion, chemical applications, hormonal disturbances, inflammation or unknown mechanisms.

Albinism is defined as the congenital

loss of pigment, partial or complete, involving the skin, hair and eyes[118]. In *partial albinism* or leukoderma there are variously sized patches of depigmentation which are well defined and do not have a hyperpigmented border. These patches usually remain unchanged for the duration of life and the hairs within them are achromic. Negroes with partial albinism are sometimes termed "pied" or "piebald." Smith and Schulz state in a recent article (A.M.A. Arch. Dermat., **71**, 591, 1955) that partial albinism is inherited as a dominant Mendelian characteristic and consists of patches of depigmentation and usually a white forelock overlying a depigmented portion of scalp. Lesions are present from birth and persons who exhibit very few or indistinctly depigmented areas are termed spotlings by Cromwell (Am. J. Hered., **31**, 94, 1940).

Complete albinism is inherited as a Mendelian recessive characteristic and is found in patients known as albinos. The entire skin surface lacks melanin and is pink. The iris is transparent or pink. Mental deficiency is often present. This disorder occurs in white and Negro patients, persists for life and occurs in families but rarely in succeeding generations. Melanocytes are present but are nonfunctional, due to lack of tyrosinase[61].

Vitiligo is an acquired cutaneous achromia characterized by variously sized and shaped patches which are milk white. They may be single or multiple, usually have hyperpigmented borders and a tendency to peripheral enlargement. When a patch of vitiligo has a red papule or brown maculopapule in its center, it is called *Leukoderma centrifugum acquisitum*. The brown lesion is usually a pigmented nevus[118]. Asboe-Hansen[8] reported that vitiliginous zones have a tendency to itch and cited a report by Quiroga *et al.* stating that histamine is increased in such areas. He also stated that mast cells were increased in areas of vitiligo and that such cells were often present in larger numbers in itching dermatoses. Rothman[134] reported the presence of hypalgesia in patches of vitiligo and some authors consider it a trophoneuritic condition. Various hormonal dysfunctions have also been incriminated in the search for the cause of vitiligo. At present it may be stated that vitiliginous skin possesses a normal complement of melanocytes which fail to produce melanin. It has also been shown that such skin has twice the normal amount of sulfhydryl[168]. Danzig[42] reported an interesting case with jaundice sparing vitiliginous areas.

The *Vogt-Koyanagi syndrome* consists of severe uveitis associated with alopecia, poliosis, dysacousia and vitiligo. There is bilateral eye involvement and the prognosis for sight is guarded. The literature on this subject was reviewed by Lockwood[104] in 1949.

Panhypopituitarism often results in pallor with loss of melanin because MSH is lacking. The action of the little functioning adrenal medulla and cortex is then of relative unimportance.

Fitzpatrick and Lerner[61] quote authorities who have found that *administration of BAL and thiouracil* may cause depigmentation of the hair and skin respectively. This is due to their high sulfhydryl content. *Ascorbic acid* inhibits the oxidation of melanin precursors and reduces melanin already produced.

Freckle cream, which has been used in the past, exerted its variable depigmentating action by virtue of its mercury content[114]. Mercury is capable of partially displacing copper from tyrosinase[45]. Mercuric and other metallic preparations may also lead to hyperpigmentation as will be seen later.

Recent writings have emphasized depigmentation of the skin due to agents they come in contact with at places of

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employment. Chief among these is the loss of melanin in areas exposed to a *rubber antioxidant* known as Agerite Alba (monobenzyl ether of hydroquinone). Ordinarily exposure must be prolonged and Negro workers are more commonly affected[117]. That this affection is not limited to those employed in industry is apparent from the reports of leukoderma due to rubber products used elsewhere. Thus housewives may be afflicted by using rubber gloves and men from hat bands, and the like. A case of leukoderma due to Agerite Alba in the cement of adhesive tape has been reported[150]. Depigmentation due to Agerite Alba occurs on areas exposed to the antioxidant and is enhanced by perspiration. The lesions are indistinguishable from vitiligo and appear in susceptible individuals, chiefly Negroes. Perifollicular areas are often spared and are the first to repigment. At times there is a preceding or concomitant dermatitis which may represent contact sensitivity. Symptoms usually persist about a year following removal from the offending compound and other antioxidants used in industry do not seem to have a similar effect[91]. The diagnosis can be aided by using a patch test containing Agerite Alba (70% in an ointment base) which is kept in place 72 hours. Depigmentation may occur in the ensuing 3 to 5 months[139].

The mechanism of action of the monobenzyl ether of hydroquinone is that of inhibiting the oxidation of tyrosine to DOPA (the first reaction of melanogenesis[45,64]). It may also contribute to the chemical reduction of melanin. The DOPA reaction is negative in affected areas and positive in unaffected areas. Compounds related to Agerite Alba such as hydroquinone (used in photographic developers) and 5.7 diiodo 8 hydroxyquinoline (used in the treatment of parasitic infestations) have been known to produce inconstant depigmentation. Hydroquinone itself is not oil soluble (therefore poorly absorbed by the skin) and is unstable chemically[64].

Schwartz[139] lists the following *alternative causes of occupational depigmentation.*

1. Areas of hyperpigmentation may eventually depigment.
2. Areas of scarring may become depigmented.
3. Areas of healed arsenical dermatitis following antisyphilitic therapy may depigment. Healed sites of occupational arsenical contact dermatitis do not do so.

Just as skin subjected to trauma or inflammatory reaction may become hyperpigmented, so it may also become depigmented. Depigmentation due to *pinta* and *syphilis* have received attention earlier in this review.

No attempt will be made to discuss *graying of the hair* since so little is actually known about it. However, artificially produced graying has been reported following ingestion of chloroquine[138] and following Roentgen-irradiation. Zeligman[183] reported 3 cases in children who had received routine epilations for tinea capitis using 365r to 5 points on the scalp. The hair was normal before epilation and gradually became flecked with gray as much as a year after treatment. These patients all had family histories of premature graying of the hair. Thus Roentgen therapy appeared to accelerate the graying process. Moshman[113] proposed that decolorization of the hair of mice be used as a Roentgen-ray dosimeter since it was quantitatively proportional to the amount of radiation. Chase[32] stated that Roentgen ray caused graying of the hair by interfering with the production of melanin by the melanocytes of the matrix or by their actual destruction.

Phenyluria or phenylpyruvic acid oligophrenia or phenylketonuria[61] is a disease characterized by mental deficiency; increased excretion of phenylpyruvic acid, phenylacetic acid and phenylalanine in the urine; and abnormally high phenylalanine levels in the blood. It is inherited as a recessive trait. Individuals so affected have fair hair, blue eyes and a blond complexion. There is a general decrease in the products of tyrosine metabolism since phenylalanine is not converted to tyrosine. The patients must then rely on exogenous sources of tyrosine for use in synthesis of adrenalin, noradrenalin, thyroxine, hemogentisic acid and melanin. Diagnosis is aided by the detection of phenylpyruvoracemic acid in the urine which turns a greenish color upon the addition of ferric chloride[131].

HEMOGLOBIN PIGMENTATIONS. Discoloration of the skin due to the influence of hemoglobin or its products is seen relatively frequently in the form of *cyanosis* due to the presence of reduced hemoglobin and *purpura* due to the presence of extravasated blood in the skin or hemosiderosis due to stasis. These, as well as the more rare discolorations due to hemoglobin, will be considered in the following paragraphs.

Bronze diabetes or hemochromatosis provides a striking illustration of the discoloration which can be produced by hemosiderin plus melanin and to a small degree, hemofuchsin. The symptoms of this disease are well known to physicians, but its etiology and treatment are obscure. In addition to references listed below Althausen *et al.*[4] and Kleckner *et al.*[93] have reviewed the subject thoroughly. The pigmentation is accentuated in areas exposed to the sun and also in the axillae, groins and about the genitals and perineum. The mucous membranes may be discolored and so do not aid in the distinction from Addison's disease[142]. The suggestion has been made that melanin pigmentation of the skin in hemochromatosis also takes place by virtue of the sulfhydryl binding power of the iron in hemosiderin[97].

Hemosiderosis, the presence of abnormally large deposits of hemosiderin in the various tissues without the production of gross lesions, must be distinguished from hemochromatosis. It may follow large numbers of transfusions or may occur in hemolytic anemias, pancytopenias and possibly leukemia. That distinction from hemochromatosis is possible by utilizing clinical and laboratory means is emphasized by Kleckner *et al*[92]. These authors state that, "transfusional hemosiderosis occurs with equal frequency among the two sexes and 25% of our patients were 25 years old or less. Cirrhosis of the liver is absent or a coincidental finding and diabetes mellitus and pigmentation of the skin occur infrequently."

These authors state further that extensive deposits of intracellular hemosiderin are infrequent in hemosiderosis, while frequent in hemochromatosis. They feel that needle biopsy of the liver is the most reliable method of diagnosis of hemochromatosis. The detection of hemosiderin in the skin following biopsy is presumptive but not diagnostic evidence for the presence of hemochromatosis.

Depositions of hemosiderin in the skin due to *venous stasis* often cause yellowish brown discoloration. Thus it is well to avoid the legs when performing a biopsy on a patient with suspected hemochromatosis.

Purpura due to a variety of causes presents a picture which is recognizable by physicians generally. Not as familiar, are the so-called *dermatologic purpuras*. In these pigmented dermatologic purpuric eruptions no systemic manifestations are found, nor are there demonstrable hematologic abnormalities.

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This group of disorders is composed of purpura annulare telangiectodes of Majocchi; peculiar progressive pigmentary disease of Schamberg; pigmented purpuric lichenoid dermatosis of Gougerot and Blum; and angioma serpiginosum of Hutchinson. These diseases affect the lower extremities for the most part and all produce punctate, pigmented macules which are at first reddish later changing to the brownish color of hemosiderin and finally fading almost completely. The dermatologic purpuras are closely related and their distinction one from the other depends upon fine clinical points. In fact, many authorities consider them to represent the same disease entity. The fundamental process is increased capillary fragility. The general health is not affected and remissions and exacerbations occur[118,126].

The *Hofstätter-Cullen*[39,76] or *Grey-Turner*[165] *sign* may afford important information regarding acute abdominal disorders. Characteristically, this sign is described[111,146] as consisting of a bluish discoloration at the umbilicus appearing a few days after the onset of acute symptoms. Ordinarily hemorrhagic fluid from the peritoneal cavity is causative but it may be seen in any condition giving rise to discolored fluid in the peritoneal cavity. The fluid is believed to follow fascial planes and openings in the abdominal wall until it finally becomes visible.

Fallon and Manning[58] emphasize the variability of this cutaneous sign with regard to location, color and cause.

Jeghers[82] listed the various *abnormal hemoglobin complexes* and the colors they produce. These are as follows:

Carboxyhemoglobin, cherry red
Nitric oxide hemoglobin, bright red (poisoning by fumes from combustion of explosives)
Methemoglobin, chocolate-blue
Sulfhemoglobin, lead or mauve-blue
Cyanhemoglobin (formed by a combination of hydrocyanic acid with methemoglobin), bright red

A number of drugs can cause methemoglobinemia and sulfhemoglobinemia (enterogenous cyanosis). At times the two conditions are present simultaneously. The patients do not have cardiac or pulmonary disease and are not dyspneic. Heredity and exposure to various chemicals are important etiologic agents. Drugs incriminated as causes of both types of abnormal hemoglobin are: sulfonamides, phenacetin, acetanilid, trional, sulfonal, pamaquin, pyridium and potassium chlorate. Stopping the drug is followed by disappearance of methemoglobinemia in a few days. Sulfhemoglobinemia may persist for a longer time. Avoidance of sulfur containing saline purgatives during sulfonamide therapy is said to reduce the morbidity of these disorders[33].

Sigmund and Shelley[125] have reported the second case of *livedo-reticularis* of the abdomen in a case of *acute pancreatitis*.

METALLIC NONMELANIN PIGMENTATIONS. Various metals, when applied locally, injected intracutaneously, or taken internally, may cause discoloration of the skin. Of these, arsenic has been discussed among the melanin pigmentations. The iron-containing pigments, hemosiderin and hemofuchsin, have also been discussed earlier. It is to be remembered that pigmentation due to any metal can be modified by the concomitant increase of melanin.

Argyria was more common in years past when the use of silver compounds was more widespread. It is the subject of a thorough monograph by Pillsbury and Hill[123]. Much of what follows may be found in their work.

Any of the silver compounds given by any route may be offenders, provided exposure is sufficiently prolonged, for the metal is accumulated in the

body over a period of years. Pigmentation is permanent and refractory to treatment. Silver is deposited in the corium and is especially prominent in the membrana propria of the sweat glands[75]. Silver particles can be demonstrated readily on darkfield examination of an unstained tissue section[5].

The color of the skin in argyria has been described as glistening slate-gray, blue-gray, or lead colored with a metallic sheen or it may be black. The clinical picture of generalized argyria, while varying in intensity, is very similar whatever the source of silver. The exposed areas are most frequently and most markedly affected. Light seems to accentuate the color. The conjunctivae and oral mucous membranes are also prominently involved.

An early sign is said to be discoloration of the nails which has often been misinterpreted to be cyanosis. The hair may assume a steel-gray color. Scars are not ordinarily pigmented. Apparently the presence of silver in the skin does not lead to any real dysfunction. Argyria must be differentiated from cyanosis due to various causes: Addison's disease, ochronosis, hemochromatosis, malignant melanoma with melanosis, bismuthia, chrysiasis and arsenical melanosis.

Of special interest to dentists and to dermatologists is the *amalgam tattoo.* This is actually localized argyria caused by accidental injection of amalgam into the buccal and gingival mucosae when the teeth are being filled. Bell *et al.*[20] have recently called attention to this condition which is not at all rare. A variable period of time following imbedding of the silver amalgam particles, grayish-blue macules appear. These have been mistaken for blue nevi or malignant tumors. Histologic examination is revealing in that, on routine hematoxylin and eosin staining, brownish pigment is seen to be deposited especially in elastic tissue fibers. Dark-field examination shows the pigment to be composed of silver particles having an affinity for elastic tissue. Similar lesions may develop when particles of silver are introduced into the skin[19] producing lesions which might be mistaken for nevi.

Generalized pigmentation due to the administration of *gold compounds* is rare. When present it is difficult to distinguish from argyria. A history of medication given by parenteral route suggests gold whereas topical application suggests silver. Erythema may precede the pigmentation of chrysiasis. Discoloration appears several months after the administration of gold, is accentuated by exposure to light and remains permanently. Lorenzen, cited by Schmidt[137], stated "that no patient receiving a total dose of less than 50 mg. of gold sodium thiosulfate per kilogram of body weight had definite chrysiasis and that no patient escaped having the condition if the total dose received was 150 mg. per kilogram of body weight." Pigmentation usually begins on the lower eyelids but occurs on any area exposed to ultraviolet radiations. The color of the skin may vary from gray, slate gray, grayish purple, grayish blue, bluish violet, blue green to brownish yellow[137]. The large metallic granules are to be found in the dermis about blood vessels and in chromatophores. They are also present in the epidermis. Dark-field examination will not disclose their presence.

Pigmentation due to *bismuth* usually involves the mucous membranes. Much less commonly a diffuse cutaneous discoloration occurs. The pigmentation most often begins at the ileocecal valve and extends diffusely throughout the colon. It may also involve the gingiva or oral mucosa as a brown, bluish, or black discoloration. Deposits of bismuth have been reported in the vagina and

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urinary bladder[170,178]. Bismuthia consists of a diffuse blue-black pigmentation of the entire skin and greatly resembles argyria[105]. The blue gum line of bismuth can often be observed adjacent to teeth in poor repair. The line usually disappears several months following cessation of therapy. Coarse bismuth particles are to be found in the chromatophores of the cutis. They are not present in the membrana propria of sweat glands. Further distinction from other metals can be made by spectroscopic means.

Hydrargyria denotes the brownish or slate colored pigmentation of the face following application of ointments containing mercury. The color is accented about hair follicles and in the folds of the skin[77]. It is especially likely to occur on the eyelids following use of mercury ointments in that location[175].

The local application of *iron salts*, such as ferric chloride or ferrous sulfate in conjunction with certain other compounds which enable the iron to precipitate in the tissues, may cause permanent brown tattoo-like pigmentation. These iron compounds have been used for acute vesicular dermatitis, especially that due to poison ivy[154,159].

MISCELLANEOUS PIGMENTARY DISORDERS. Tattooing is an art traceable to ancient societies and was the subject of an extensive review in this journal by Beerman and Lane[16]. The operation consists of the introducing of foreign pigments into the dermis for the purpose of producing colored designs. The various substances utilized have been listed by Rostenberg *et al.*[130]. Aside from its decorative use, the tattoo has been employed in an attempt to cover such blemishes as port wine stains. The various pigments differ in their degrees of permanence. It is most often true that it is a great deal easier to acquire a tattoo than it is to be rid of one. *Foreign particles* when directed at the skin under high pressure (explosion, compressed air, and the like) may become embedded in the dermis and give a permanent discoloration. Such occurrences constitute an industrial hazard.

The term *taches bleúatres* has been used to describe the small bluish stains found on the chest, abdomen, thighs and upper arms in patients with pediculosis pubis. They are believed to result from the action of the parasite and have also been called maculae ceruleae. Minute blue spots are often found at sites of injection and are stigmata of drug addiction. The color is probably produced by small metal or carbon fragments placed rather deeply in the skin upon injection of drugs[118].

The phenomenon of "*black dermographism*" was first described in the Russian literature and later studied by Urbach and Pillsbury[167]. The term is actually a misnomer since it involves the production of a dark line on the skin, rough paper, or wood by stroking with certain metals. An abrasive powder, harder than the metal used, is necessary. Such powders are present in cosmetics as well as in smoke from some factories. The phenomenon depends upon friction between the metal and the powder. Metals which may give rise to this dark line are as follows: silver, copper, aluminum, nickel, zinc, tin, lead, brass and gold of less than 18 carats. Iron, platinum and gold finer than 18 carats produce negative results. Various substances may serve as the powder to react with the above metals. Two of the most common, titanium dioxide and calcium carbonate, are found in face powders and react most strongly. The black line is easily removed from the skin.

Ochronosis is a symptom complex occurring in patients with alkaptonuria. The chief features are arthritis, especially of the spine, pigmentation of the

cartilages and sometimes of the skin, and urine which darkens on standing. Homogentisic acid, a tyrosine metabolite, is normally degraded to acetoacetic acid and fumaric acid before being eliminated by the body as carbon dioxide and water. Patients with alkaptonuria are incapable of completing this process and homogentisic acid is excreted instead. Fewer than 200 cases of alkaptonuria have been reported, and of these, only half had ochronosis[95]. The disease is more common in males and is believed to be transmitted as a recessive trait in most cases[69].

The cartilages are darkly stained, appearing bluish through the skin, and feel firm and rigid. Granular or diffuse deposits of homogentisic acid can be found in any cartilage, though smaller joints are not usually affected.

The skin exhibits a mottled brown or blue pigmentation about the neck, head, torso and extremities. The axillae and the genital regions may be the sites of a bluish green color due to pigment from the sweat and sebaceous glands. Pigmentation of the finger nails is rare. Discoloration of the lids, conjunctivae and oral mucosa have been reported. The disease is frequently recognized by a bluish color of the ears. At times the only color change may be a gray-blue discoloration of the sclerae[149]. Grayish-blue staining of the fibrous tissues and tendons is best seen about the knuckles and knees and on the dorsa of the feet. It appears that the pigment responsible for the above color changes is a product of homogentisic acid by polymerization. Various internal organs may be affected by pigment deposits.

Homogentisic acid is a potent reducing substance so that the urine from such patients may give positive Benedict's reactions for sugar. The urine will darken a photographic plate. It is literally true that a photograph of a patient with alkaptonuria may be developed in his own urine. This occurs in no other known disease. Darkening of the urine may be accelerated by the addition of sodium hydroxide[108].

Exogenous alkaptonuria has been reported due to excessive use of carbolic acid dressings. This is almost unheard of at present, but Wooley[181] encountered such a case in 1949. Poisoning due to benzene and its derivatives has also been incriminated.

Various *dyes* used medically in diagnosis and treatment may produce localized discolorations if injected into the tissues, that is, outside a vein. Some of these are Congo red, methylene blue, Evans blue, and others.

The term *chloroma* has been used to describe green tumors which used to be seen more commonly than now. They generally occur about the face and head in children with leukemia, usually myelogenous in type. Humble[78] reported 2 cases associated with myelogenous leukemia in young adults and one in a middle-aged woman with monocytic leukemia. He attributed the pigmentation to choleglobin. An increase in porphyrins has been reported in the tumor tissue of chloroma[33].

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PHYSIOLOGY

PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF DECEMBER 20, 1955

INFORMAL SEMINAR ON RENAL PHYSIOLOGY

J. K. CLARK, M.D. (Department of Medicine, University of Pennsylvania): **Introductory Remarks.** The program for this evening as arranged by our Secretary consists of an informal seminar on renal physiology. If one classifies the functions of the kidney into: 1) urine formation, 2) systemic hemodynamic adjustments and 3) the poorly understood endocrine metabolic function such as gluconeogenesis, production of sero principles, and the like, we find that tonight's symposium is exclusively concerned with the first, that is, the process of urine formation. The historic aspects of this problem are familiar to most of us. It was obvious to all early observers that urine differed from plasma water in many important respects as to concentration of a variety of substances, some substances being present in much greater concentration in urine than in plasma water, while others much greater in plasma water and absent (if present at all) in the urine. In the face of these undisputed facts a bitter wrangle ensued over the mechanism whereby the kidney produced these changes, whether by some sort of secretory vitalism or in accord with principles of physical chemistry. It remained for A. N. Richards and his group in the Department of Pharmacology at the University of Pennsylvania to establish, on the basis of unequivocal evidence, the existence of glomerular filtration as a blind physical force relying on the energy of the heart, supplemented by tubular reabsorption of many important substances. Whether in addition to these two demonstrated processes a third process, namely, tubular secretion, actually existed remained unsettled until Marshall demonstrated its existence in the aglomerular goose fish.

At the present time tubular secretion is a well accepted fact, not only for foreign substances such as penicillin, phenol reds, para-aminohippurate, but for a few substances present physiologically, such as potassium. This demonstration has been possible in intact animals, including man, by the availability of a reliable measure of glomerular filtration rate, namely, inulin clearance. Recently, however, the possibility has been suggested that many substances may be handled by a three-component system, namely, filtration plus reabsorption plus secretion, the balance between these components determining the net over-all excretory effect. Potassium seems to be one substance handled by such a three-component system.

The program tonight concerns itself with both glomerular and tubular processes, and should inevitably lead us into an interesting discussion of many of the yet unsolved problems of excretory mechanisms of the kidney.

A Fluorescence Technique for the Evaluation of Glomerular Intermittence in Mammals. M. E. HARTMAN, M.D., and A. F. FLAGG, A.B. (Department of Anatomy, Temple University School of Medicine.) Previous studies

were conducted on the kidney of the 4 to 5 gm. immature mouse, using the quartz rod method of transillumination. At that age more anatomically mature glomeruli lie on the surface than at any other time. These studies revealed that total glomerular intermittence was rare but capillary intermittence common in this group. In order to evaluate these findings in relationship to the mature mammal we modified a technique developed by Moses and Schlegel. This technique consists of the intravenous injection of Vasoflavine, a water-soluble fluorescent dye, which has a specific affinity for the endothelium and hence labels any vessel through which plasma is flowing. The dye is injected into the inferior vena cava and remains in the circulation for approximately the circulation time of the species being studied. The kidney is then removed and free hand sections placed in Stender dishes of glycerin. They are then examined in incident ultraviolet light with a peak emission at 3,650 angstrom units. The addition of a calibrated reticule to the ocular of the microscope enables one to count the number of glomeruli open to the flow of plasma for the short time interval and this figure can then be converted to the number of glomeruli per square millimeter. The area counted was standardized by counting the glomeruli in successive fields, keeping one edge of the reticule on the capsular margin of the kidney.

Using this technique an average normal glomerular count per square millimeter was established for the mouse, rat and dog. This average number could be increased by a statistically significant increment by treating the animal with Apresoline or Regitine. The results indicate that in the normal mouse, rat and dog all of the glomeruli are not functioning at all times.

Relationships between pH, Chloride and Inulin in Proximal Tubule Fluid of Necturus Kidney.* GERHARD GIEBISCH, M.D.** (Paper given by PHYLLIS A. BOTT, PH.D.). (Department of Physiological Chemistry, Woman's Medical College of Pennsylvania). Micropuncture studies such as those conducted by Walker *et al.* (Am. J. Physiol., **118**, 121, 1937) have indicated that the chloride concentration of proximal tubule fluid is almost always higher than that of serum. With no increase in tubular osmotic pressure these results possibly imply preferential reabsorption of bicarbonate and, assuming equal pCO_2 in serum and tubule fluid, some proximal acidification. To investigate the relationship between chloride concentration and acidification, simultaneous measurements of chloride, inulin and pH were carried out on samples of fluid obtained by micropuncture from proximal tubules of Necturi. The concentration of inulin in tubule fluid always exceeded that of serum, indicating reabsorption of fluid from this part of the nephron. The results obtained indicate that the proximal tubule does not participate in urinary acidification and confirm the findings of Montgomery *et al.* (Am. J. Physiol., **118**, 144, 1937). The concentration of chloride in proximal tubule fluid when treated with deproteinizing agents was found to be not significantly higher than that of the serum. Thus no evidence of preferential reabsorption of bicarbonate could be demonstrated in this species. The results presented resolve some of the discrepancies of earlier micropuncture studies and are in good agreement with known data on osmotic pressure and sodium concen-

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trations in proximal tubule fluid of Necturus.

Renal Elimination of 3-Methylaminoisocamphane Hydrochloride (Mecamylamine). JOHN E. BAER, PH.D., SUE F. PAULSON, B.A., HORACE F. RUSSO, B.S., and KARL H. BEYER, M.D., PH.D. (Pharmacology Section, Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa.). Mecamylamine is a potent, orally absorbed ganglionic blocking agent. The amine is a strong base ($pK_a = 11.4$) which can be determined in biological fluids by a methyl orange dye method. Experiments designed to study the fate of mecamylamine, including its mode of renal elimination, were performed in trained unanesthetized dogs. Under customary conditions, the renal clearance of mecamylamine exceeded glomerular filtration rate (GFR) in two dogs, but was substantially lower than GFR in two others. In a dog rendered acidotic by the oral administration of ammonium chloride, mecamylamine was excreted at 4.2 times the GFR; when sodium bicarbonate was given to the same dog, the ratio was 0.07. Additional experiments were performed to study the factors influencing this shift from net active tubular secretion to net active tubular reabsorption. Stepwise increase in the concentration of infused bicarbonate caused a decrease in mecamylamine clearance ratio from 3.9 to 0.28 times the GFR. Acetazoleamide (#6063), which produces alkaline urine but not systemic alkalosis, caused the same reduction in clearance ratio. Simultaneous clearance and renal extraction of mecamylamine, creatinine and p-aminohippurate in a unilaterally nephrectomized dog provided direct evidence of decreased A–V drug plasma concentration with increased urine pH. High doses of p-aminohippurate did not depress tubular secretion of mecamylamine, nor did mecamylamine at the doses studied (2.5 to 7.5 mg./kg.) influence GFR or (PAH) renal plasma flow.

The Renal Excretion of Magnesium. E. S. BARKER, M.D., J. K. CLARK, M.D., and J. R. ELKINTON, M.D. (Department of Medicine, University of Pennsylvania). Next to potassium, magnesium is the cation present in greatest concentration in intracellular fluid, but much less is known of its behavior. Urinary magnesium excretion rate (UV_{Mg}) averaged 7.0 microequivalents per minute during control periods in 33 studies by usual clearance techniques in 24 normal young men. Hypertonic sodium lactate given intravenously (2.4 mEq./kg., 0.9 M., 10 minutes, 6 subjects) evoked a small increase in UV_{Mg} expressed in absolute terms; however, expressed as percentage of control rates it was 221 ± 56 (S.D.) % during infusion, and 261 ± 84% ten minutes later, then falling rapidly and reaching control rates within 1½ hours.

The lactate-induced increase in UV_{Mg} could not be explained by acid-base changes in either blood or urine. Equivalent intravenous sodium bicarbonate resulted in significantly smaller rise in UV_{Mg}, although acid-base effects and rise in potassium excretion (UV_K) were greater. Diamox caused slight metabolic acidosis and no increase in UV_{Mg}, although increase in UV_K and urinary pH were at least as great as following lactate.

The UV_{Mg} response could not be accounted for by release of magnesium from cells following lactate administration, since there was a slight decrease (not demonstrably significant) rather than an increase in plasma concentration.

Changes in glomerular filtration rate, renal plasma flow and rate of urine formation were small and in opposite directions in individual cases following

lactate, although the rise in UV_{Mg} was uniformly present.

The data might be explained on the basis of a three component system of magnesium filtration, reabsorption and secretion. Clearly reabsorption is normally the dominant tubular component since, even with liberal allowance for protein binding, the filtered load greatly exceeds urinary excretion of Mg. If the postulated secretory component exists, it could perhaps, although small, have an important regulatory role. Many factors which influence para-aminohippurate transport appear related to certain changes in UV_{Mg}, although the nature of the relationship has not been clearly shown.

SUMMARIO IN INTERLINGUA

(See page 389 for original article)

Tractamento de Infectiones del Vias Urinari con Triple Sulfonamidos Sol e Miscite con Penicillina

Un Studio Comparative

Esseva executate un studio clinic e bacteriologic in 148 patientes visitante, includente 98 pro cento femininas adulte, pro comparar le efficacia de duo preparatos oral, un mixtura de tres sulfonamidos e un mixtura de benzathinopenicillina e tres sulfonamidos, in non-complicate infectiones acute e chronic del vias urinari. Ante le comenciamento del medication, specimens de urina esseva obtenite per catheterisation e subjicite a examines microscopic e culturas. Le presentia de varie organismos esseva demonstrate. *Escherichia coli* esseva presente in 65 pro cento del casos.

Le medication esseva administrate in un dose initial de 2 g, sequite per 0,5 g 4 vices per die pro un periodo de 7 dies. (Le dose usualmente prescribite de sulfonamidos es duo vices iste quantitate o plus.) Septe dies post le fin del curso, omne patientes recipeva un routinari examine urologic con studio laboratorial de urina.

Esseva observate nulle significative differentia in le efficacia del duo preparatos usate. Ex 71 patients tractate con le mixtura de sulfonamidos, 79 pro cento esseva liberate ab lor infection urinari; in 21 pro cento de illes, le organismo infective esseva resistente al therapia. Ex le 77 patientes qui recipeva le combination de sulfonamidos con penicillina, 75 pro cento esseva tractate con successo; in 25 pro cento le infection persisteva.

Ambe preparatos esseva active contra le infectiones coccal. Le triple sulfonamidos eradicava *Proteus vulgaris* in 6 inter 7 casos.

Le combination de penicillina con sulfonamidos esseva plus efficace que le triple sulfonamidos sol in prevenir crescentias secundari de organismos non presente in culturas pre-tractamental.

Reactiones de sensibilitate (mal de capite, frigido, eruptiones cutanee, tumescentia e rubor del lingua) occurreva in 2 pro cento del casos sed dispareva promptemente post discontinuation del therapia antibacterial e le initiation de mesuras supportative. Il non habeva ulle signo de crystalluria, in disturbationes gastrointestinal o altere series effectos lateral.

BOOK REVIEWS AND NOTICES

THE TUBERCLE BACILLUS IN THE PULMONARY LESION OF MAN: HISTOBACTERIOLOGY AND ITS BEARING ON THE THERAPY OF PULMONARY TUBERCULOSIS. By GEORGES CANETTI, M.D. Pp. 226; 48 ills. New York: Springer Publishing Co., 1955. Price, $8.50.

SOME insight into the importance of this work may be inferred from the fact that it was translated into English at the suggestion of René Dubos and Walsh McDermott, who have also written a foreword as well as aided in the text translation. Its value is primarily due to the author's broad approach to the subject, integrating both histologic and bacteriologic knowledge of tuberculous infections. The material is presented in five chapters: 1) Histology of Tuberculosis: A Review; 2) The Tubercle Bacillus in the Pulmonary Tuberculosis Lesion; 3) The Histobacteriogenesis of Tuberculous Lesions: Experimental Studies; 4) Tuberculous Lesions and Immunity: and 5) Tuberculous Lesions and the Therapy of Tuberculosis. The illustrations are excellent and in keeping with the over-all excellence of the volume.

This book is highly recommended to all physicians and investigators interested in the field of tuberculosis and its treatment.

C. Z.

THROMBOSIS AND EMBOLISM. Proceedings of the 1st International Conference, Basel, 1954. Edited by TH. KOLLER AND W. R. MERZ, University of Basel. Pp. 1316; illustrated. Basel: Benno Schwabe & Co., 1955. Price, Fr. 76.

THIS large volume presents the 254 contributions including lectures, 8 film texts and 39 scientific exhibits that were presented at the First International Conference on Thrombosis and Embolism held in Basel on the 20th to 24th of July, 1954. They are grouped in some eighteen sections dealing with such subjects as The Physiology and Pathophysiology of Coagulation, The Chemistry and Pharmacology of Anticoagulants, Pathogenesis and Pathophysiology of Thrombosis, Pathologic Anatomy and Experimental Pathology, Symptomatology and Diagnosis and Conservative Therapy of Thrombosis, Surgical Therapy of Thrombosis, Anticoagulant Therapy, Therapy with Fibrinolytic Substances, The Prophylaxis of Thrombosis, Sequelae, Statistics, Anticoagulants in Diseases of the Arteries and a number of panel discussions. The papers are written for the most part in English, some are in French and some in German. Each paper has abstracts in English, French and German. This is a most valuable production in an important field and should find a warm welcome from a wide range of physicians.

R. K.

LEHRBRUCH DER PRAKTISCHEN ORTHOPÄDIE. By DOZENT DR. W. ABERLE, PROF. DR.PH. ERLACHER, DR. A. HARTWICH, DR. A. KOENIGSWIESER, AND PROF. DR. O. STRACKER. Pp. 540; 715 ills. Wien-Bonn: Wilhelm Maudrich, 1955. Price, $24.50.

THIS textbook is dedicated to Prof. Hans Spitzy, formerly professor in Orthopedic Surgery in Vienna, by his students. Prof. Dr. Ph. Erlacher is Director of The Orthopedic Hospital in Vienna, his associates are members of his staff. Their combined task was to deal with Orthopedics by reflecting and emphasising the teachings of the school of Dr. Spitzy, on one hand, and by approaching the vast subject by dividing it into three chapters according to age groups, on the other. They accomplished both objectives efficiently.

Dividing Orthopedics according to age groups into Children's Orthopedics from birth to age 12, Chapter 1; into Orthopedics of Adolescents, from 12 to 20, Chapter 2; and Orthopedics in Adults after the age of 20, Chapter 3; is a desirable, practical method and has many good points. It is particularly valuable for the young student in Orthopedic Surgery. There is a brief chapter included concerning the handling of some of the orthopedic problems in Geriatrics.

The discussion of Orthopedics naturally reflects the European attitude. There are ample references to American literature but only up to 1941. The management of slipped capital femoral epiphysis, idiopathic scoliosis in this textbook has not reached our standard as yet.

Most of the orthopedic subjects are discussed with authority, and the conservative management of several joint affections will be of interest also to the older student in Orthopedics. This book is primarily recommended to the student starting his training in Orthopedics. The illustrations are fair.

O. K.

THE CEREBROSPINAL FLUID. By S. LUPS, M.D., Medical Director, Municipal Hospital, Rotterdam, and A. M. F. H. HAAN, Head of the Biochemical, Cytological and Bacteriological Laboratory Sanatorium "Oranje Nassau's Cord" Renkum (The Netherlands). Pp. 350; 93 ills. Houston: Elsevier Publishing Co., 1955. Price, $9.50.

THIS book is devoted entirely to the cerebrospinal fluid. There is an interesting introduction by Pearce Bailey in which is given the historical development of contributions toward the study of cerebrospinal fluid. The text material itself is presented in four major sections: 1) Anatomical and physiological observations; 2) the puncture of the cerebrospinal fluid; 3) investigation of the cerebrospinal fluid as an aid in diagnosis; and 4) methodology.

The various topics are comprehensively discussed, although in this reviewer's opinion, there is not sufficient attention given to the viral encephalitides and meningo-encephalitides. In this connection, the subject index also appears to be lacking as it fails to list certain disorders which are mentioned in the text. Despite these criticisms, however, this volume should be of value to neurologists, psychiatrists, internists, and clinical pathologists. C. Z.

ELECTROCHEMISTRY IN BIOLOGY AND MEDICINE. Edited by THEODORE SHEDLOVSKY, Rockefeller Institute for Medical Research. Pp. 369; 140 ills. New York: John Wiley & Sons, Inc., 1955. Price, $10.50.

THIS book is an outgrowth of the Symposium on Electrochemistry in Biology and Medicine held in New York during the 103rd meeting of the Electrochemistry Society in April, 1953. The book is not of particular interest to the general practitioner, but will be useful to those interested in fundamental bioelectric phenomena, or in the fundamentals of applications such as electrocardiography and electroencephalography. Chapter titles and authors are:

1. Introduction, Theodore Shedlovsky; 2. Membrane Potentials in the Donnan Equilibrium, David I. Hitchcock; 3. Transport of Ions across Charged Membranes, George Scatchard; 4. The Electrochemistry of Porous Membranes, Karl Sollner; 5. Membranes of High Electrochemical Activity in Studies of Biological Interest, Karl Sollner, Sheldon Dray, Eugene Grim, and Rex Neihof; 6. Dynamic Negative Admittance Components in Statically Stable Membranes, Otto H. Schmitt; 7. Ions, Potentials, and the Nerve Impulse, Kenneth S. Cole; 8. The Nature of the Electrochemical Potentials of Bioelectric Tissues, Harry Grundfest; 9. Molecular Basis for Generation of Bioelectric Potentials, David Nachmansohn and Irwin B. Wilson; 10. Some Electrical Properties of Large Plant Cells, L. R. Blinks; 11. Apparent Violations of the All-or-None Law in Relation to Potassium in the Protoplasm, W. J. V. Osterhout; 12. Diffusion in Liquids and the Stokes-Einstein Relation, L. G. Longsworth; 13. Hydrogen Ion Titration Curves of Proteins, Charles Tanford; 14. Determination of Ionic Activity in Protein Solutions with Colodion Membrane Electrodes, Charles W. Carr; 15. Activity Coefficients of Some Sodium and Potassium Phosphates in Aqueous Solutions, Fred M. Snell; 16. Polarographic Behavior of Various Plasma Protein Fractions, Otto H. Müller; 17. Some Observations on Electrocardiographs and Electrocardiographic Leads, Franklin D. Johnston and Jerome F. Cordes; 18. Preoperative Electroencephalographic Localization of Brain Tumors, B. K. Bagchi; 19. Electrical Signs of Epileptic Discharge, Herbert H. Jasper. R. H.

CYTOLOGIE DES WEIBLICHEN GENITALKARZINOMS. By DR. EDMUND SCHÜLLER, Leiter des Laboratoriums der II. Universitäts-Frauenklinik Wien. Pp. 129; 67 ills. Vienna-Bonn: Wilhelm Maudrich, 1955. Price, $6.00.

THIS excellent monograph is an enthusiastic report on the experiences with exfoliative cytology obtained at the II. Universistäts-Frauenklinik at Vienna. The author agrees with Ayre and others that this is the best method available for early recognition of cervical carcinoma, but that it is of little help in the diagnosis of uterine carcinoma. Following the introduction of this method the percentage of their stage I carcinomas rose from 17.3 to 35.3 while that of their stage II cases fell from 39.4 to 24.7. However, Dr. Schüller emphasizes that this method is time-consuming and expensive, and that it requires the services of a specially trained staff. W. E.

IONOGRAPHY. By HUGH J. MCDONALD, D.Sc., Professor of Biochemistry, Stritch School of Medicine of Loyola University. Pp. 268; 29 ills. Chicago: Year Book Publishers, Inc., 1955. Price, $6.50.

THIS volume summarizes present-day knowledge of electrophoresis in stabilized

media. Principal emphasis is placed on paper-stabilized electrolytes, although work on ion or particle migration in electrolytes stabilized with nonpaper materials is also reviewed. The author and his collaborators have made valuable contributions to this important technique of study. In this text, they not only describe equipment and methodology, but also bring out various implications and practical applications of this method of study. The comprehensive bibliography lists 865 papers on the subject.

Anyone working with, or planning to use, paper electrophoresis will find much helpful information in this book. C. Z.

ANALYTICAL CYTOLOGY. METHODS FOR STUDYING CELLULAR FORM AND FUNCTION. Edited by ROBERT C. MELLORS, M.D., PH.D., Graduate School of Medical Science, Cornell University Medical College. Pp. 509; 145 ills. New York: The Blakiston Division, McGraw-Hill Book Co., Inc., 1955. Price, $15.00.

A NUMBER of newer methods for studying cellular form and function have been brought together in this volume. The eleven contributors are all recognized authorities on their respective topics of discussion. The methods considered include the following: 1) Cytophotometric analysis in the visible spectrum; 2) histochemical and cytochemical staining methods; 3) phase-contrast, interference-contrast, and polarizing microscopy; 4) ultraviolet microscopy and microspectroscopy; 5) fluorescence microscopy; 6) electron microscopy of tissue cells; 7) radioautography in cytology; 8) historadiography; and 9) *x*-ray diffraction techniques and their application to the study of biomolecular structures.

Research workers in basic aspects of medical and biological sciences will find this a valuable reference text. C. Z.

THE PRACTICE OF DYNAMIC PSYCHIATRY. BY JULES H. MASSERMAN, M.D., Professor of Neurology and Psychiatry, Northwestern University. Pp. 790. Philadelphia: W. B. Saunders Co., 1955. Price, $12.00.

AFTER nearly 10 years the author has given us a second book embodying his concepts of the principles and practice of psychiatry. Dr. Masserman has attempted to place in a comprehensive system concepts which he prefers to call "*Biodynamics.*"

Part I of the present volume deals with the interviewing and examination of the patient to the end that the student and physician shall be well acquainted with all the assets and liabilities which will tend to modify prognosis and therapy.

Part II deals with syndromes and case discussion with Part III breaking down case exposition further for special use by various people in need of this material, such as medical consultants, marital counsellors, jurists, insurers, and others with whom the physician must deal in his daily practice. This is a somewhat unique departure from previous textbooks and should prove highly useful.

Part IV is theoretical and interestingly presented while Part V deals extensively with therapy. All types of therapy are covered in a way that should satisfy those who have deplored psychiatry's lack of emphasis on therapy. There is a stimulating chapter in this section on Biodynamics and Social Issues. There is an appendix on the training of a psychiatrist and an extensive bibliography. O. E.

PATHOLOGY FOR THE SURGEON. BY WILLIAM BOYD, M.D., University of British Columbia. 7th ed. Pp. 737; 547 ills., including 10 in color. Philadelphia: W. B. Saunders Co., 1955. Price, $12.50.

DR. BOYD'S first text in pathology appeared in 1925. Since that time there have been five editions and the last is certainly the best, not only from the standpoint of content but from that of arrangement, lucid exposition and mastery of writing. A great many pathologists have labored over their manuscripts since Dr. Boyd began to write, but none have achieved the readability, the simplicity and the charm which apparently comes so naturally to this author. Some have complained that unbiased accounting and complete coverage suffer in this atmosphere. It is hardly a fair criticism of Dr. Boyd's work for he is a wondrously wise pathologist and by avoiding the dusty medium of the unimaginative scholar he does not necessarily adopt the fancy of the novelist. By a judicious wedding of the two he produces a good text which is a delight to read, an objective which few medical authors have ever achieved.

Much of the text is newly written and the whole is fresh and modern. For the young surgeon who wants to increase his knowledge in the basic fundamentals of his specialty, this reviewer can recommend no other single source so highly. E. A.

HISTOLOGIE DER HAUTKRANKHEITEN. By OSCAR GANS AND GERD-KLAUS STEIGLEDER, Universität Frankfurt a.M. 2nd ed. Pp. 726; 258 ills. Berlin: Lange & Springer, 1955. Price, DM 285.

IN recent years, the subspecialty of dermatopathology has attained a place of prominence largely as the result of the interest of certain dermatologists and the publication of books on this subject by dermatologists and general pathologists. Gans, the first edition of whose book was published in 1925, has been a great force in this development. A direct "descendant" from some of the masters of the past, Gans has carried on the tradition of his teachers and has made positive contributions of his own to this field.

The present volume is the first of a projected series on the anatomy and development of the skin; postmortem observations in normal and diseased skin; certain dermatopathies (dystrophies) and dermatitides. There is a copious bibliography both German and other and a good index. There are 258 illustrations, mostly in color. Many of these are paintings rather than photomicrographs. Clinical photographs are conspicuous by their absence. This book is constructed on a high scholarly plane and for the novice may be completely confusing. For the general pathologist, the lack of clinical illustrations is a major defect. Also, more histologic plates would enhance the value of the presentation for all who would be interested in this subject. Furthermore, the American pathologists who study hematoxylin and eosin-stained preparations for routine work would be better served if the illustrations were from tissues prepared by this technique.

For the student of dermatopathology, who on occasion meets with unusual problems, this is a particularly welcome source book.

H. B.

CELLULAR METABOLISM AND INFECTIONS. Edited by E. RACKER. Pp. 196; illustrated. New York: Academic Press, Inc., 1954. Price, $4.80.

THE papers collected in this volume were presented at a symposium which was held at the New York Academy of Medicine in March, 1954. The material is presented in two sections: Part I, on comparative biochemistry, deals with differences in structural and metabolic patterns in hosts and parasites; while Part II is concerned with metabolic aspects of the infectious process itself. The 19 contributions, which are written by outstanding investigators, will be of value to virologists, bacteriologists, biochemists, pathologists and others who are interested in obtaining a better understanding of the importance of the metabolism of the host and of the infectious agent in disease processes.

C. Z.

SEX IN CHRISTIANITY AND PSYCHOANALYSIS. By WILLIAM GRAHAM COLE. Pp. 329. New York: Oxford University Press, 1955. Price, $4.00.

THIS is a clear and scholarly exposition of Christian religious thought through the ages on the interpretation of sex as apposed to what might be called nonreligious thought, born of psychological science, with Freud as the outstanding exponent.

Part One deals with interpretation of sex in Christianity as expounded by Jesus and Paul, Augustine, Thomas Aquinas, Luther and Calvin and then surveys contemporary Catholic and Protestant thought. Part Two deals with the interpretations of sex in psychoanalytic thought, by both Freud and contemporary analysts. Part Three deals with a reconstruction indicating how earlier theologians were much more afraid of sex impulses than those of today. It indicates how much of the restrictive sexual commands were made by bachelor celibates. It shows how the evolution of Christian thought has tended to integrate sex life more completely into the whole man and the whole of his life. Current thinking, says the author, gives sex a more divinely utilitarian role in man's efforts to progress rather than labeling it an evil force to be prohibited and inveighed against.

A most clear and comprehensive summary orients the physician and student of social sciences in the history and present position of sex in both philosophy and everyday life.

O. E.

GERIATRIC ANESTHESIA. By PAUL H. LORHAN, M.D., Professor of Anesthesiology, Department of Anesthesiology, University of Kansas Medical Center. Pp. 90, Springfield, Ill.: Charles C Thomas, 1955. Price, $3.25.

WITH the gradual prolongation of the mean span of life there has been a great need for a better understanding of the problems presented to the anesthesiologist by the elderly patient undergoing surgery and anesthesia.

Dr. Lorhan has compiled a wealth of information in a brief and complete manner. This text has been written in ten sections all of which are excellent.

The section on "The Physiologic Changes in the Aged" is very well done and deals with such subjects as: bone changes, cardiovascular changes, respiratory changes, nervous system changes and blood changes.

In the section on "Preoperative Preparation" he stresses the importance of concerning ourselves with the reversible changes such as water and electrolyte balance rather than the irreversible changes such as arteriosclerosis, hypertension, kidney and liver disease.

Dr. Lorhan in the sections on "Preanesthetic Medication" and "Anesthetic" stresses the importance of avoiding circulatory and respiratory depression, the maintenance of a patent airway, adequate oxygenation, and an even plane of surgical anesthesia and the replacement of blood as lost.

The importance of skill and judgment in the anesthetic management of the elderly patient is noted in several places.

This monograph should be read by all physicians who are treating the elderly patient. L. K.

LISTERIOSE. By Dr. Heinz Seeliger, Hygiene Institute of the Friedrich-Wilhelms University, Bonn. Pp. 152; 27 ills. Leipzig: Johann Ambrosius Barth, 1955. Price, DM 11.60 ($2.76).

LISTERIOSIS is an uncommon infection of man but a frequent one among lower animals. This monograph covers both the human and veterinary aspects thoroughly and probably is the best of the available reference volumes on infections due to the genus Listeria. Bacteriologic and serologic diagnosis is likewise covered in detail. E. S.

CONNECTIVE TISSUES. TRANSACTIONS OF THE FIFTH CONFERENCE, FEBRUARY, 1954. Edited by CHARLES RAGAN, M.D., Columbia University College of Physicians and Surgeons, Pp. 222; 55 ills. New York: Josiah Macy, Jr. Foundation, 1954. Price, $4.25.

THIS is a report of the fifth and final conference between leaders of various disciplines whose work is converging on the various problems presented by the connective tissues. The present volume maintains the high standards of interest and information set by the previous volumes. The chapter on "Introductory Remarks" is a well-edited record of free discussion of the work in progress by those participants who did not at this time present formal papers. Three detailed reports were presented, namely, "The Exchange of Materials Between Blood Vessels and Lymph Compartments" "Interstitial Water and Connective Tissues" and "Hormonal Effects on Connective Tissues," each being followed by a full and free discussion. A 39-page index follows the last discussion. This book will be of great value to all those working in the field of connective tissues at a fundamental level. J. L.

A HANDBOOK OF HOSPITAL PSYCHIATRY. A PRACTICAL GUIDE TO THERAPY. By LOUIS LINN, M.D., Assistant Attending Psychiatrist, Mount Sinai Hospital, New York. Pp. 560. New York: International Universities Press, Inc., 1955. Price, $10.00.

THIS book lives up to its title in the sense that it deals simply and practically with the many psychiatric problems in either a general or a psychiatric hospital. Its 560 pages indicate that it is not a handbook in the usual sense of the word. Its size alone testifies to the number of psychiatric problems which have to be dealt with in the average general hospital daily. Part One of the book deals with various aspects of therapy from group activity to the therapy to be derived from food. Part Two deals with the various people involved in therapy such as the nurse, chaplain, social worker, psychologist, attendant and volunteer worker.

Part Three deals with the different types of patients such as the pregnant patient and the addict. Part Four contains chapters on administration, research and forensic problems. Part Five discusses relatives, family care and educating the public. There are appendices on such subjects as classification of mental disorders, reading materials in a group psychotherapy program and a home-training program for retarded children. This is one of the most practical books on psychiatry for the general physician, to appear in a long time. O. E.

Surgical Forum, Clinical Congress of the American College of Surgeons. Committee on Forum on Fundamental Surgical Problems of the American College of Surgeons, Harris B. Schumaker, Jr., F.A.C.S., Indianapolis, Chairman. Volume V. Pp. 851; illustrated. Philadelphia: W. B. Saunders Co., 1955. Price, $10.00.

THIS volume presents, in a condensed and readable form, the papers presented at the Forum on Fundamental Surgical Problems.

Clinical Congress of the American College of Surgeons, in Atlantic City, in November, 1954.

The papers are grouped together under the various body systems and consist, for the most part, of the experimental surgical work that is being carried out in the various surgical laboratories throughout the country. The illustrations are adequate and plentiful, and the volume deserves a place in the library of every surgeon.

This book would likewise be of considerable interest to internists and others in nonsurgical specialities who are interested in investigative and experimental medicine. H. C.

NEW BOOKS

Perinatal Mortality in New York City. Analyzed and Reported by SCHUYLER G. KOHL, M.D., D.P.H., State University of New York College of Medicine. Pp. 112. Cambridge, Mass.: Harvard University Press, 1955. Price, $2.50.

THIS little book is a part of the product of the work of the Subcommittee on Neonatal Mortality appointed by the Committee on Public Health Relations of the New York Academy of Medicine. The committee was headed by Dr. N. C. Foot. The material was analyzed by the author and published for The Commonwealth Fund.

Nine hundred and fifty-five cases of perinatal deaths were analyzed from a variety of angles. The material as presented is somewhat disappointing, largely because no comparisons are made on the basis of survival and death statistics. The book will be of most interest to those conducting similar analyses in infant mortality series. E. A.

Cardiology Notebook. By ALFRED P. FISHMAN, M.D., M. IRENE FERRER, M.D., REJANE M. HARVEY, M.D., JOHN H. LARAGH, M.D., DICKINSON W. RICHARDS, M.D., AND JOSEPHINE S. WELLS, M.D. Pp. 97; 40 ills. New York: Grune & Stratton, Inc., 1955. Price, $2.50.

A TEACHING aid for beginners as used in the College of Physicians and Surgeons of Columbia University. There are sections on cardiac fluoroscopy and roentgenology, electrocardiography, hemodynamics and nomenclature of the cardiac diseases. It should be useful in class exercises. R. K.

Über die Wandelbarkeit innerer Krankheiten. By PROF. DR. GUSTAV BODECHTEL. Pp. 32; 8 ills. Munich: J. F. Lehmanns Verlag, 1954. Price, DM 2.

IN this lecture, delivered in honor of the eightieth birthday of Professor Alfred Schittenhelm, the author discusses in a very interesting and stimulating fashion the changing clinical pictures in a variety of diseases and the various possible causes of such changes. Those who read German will find it entertaining and instructive. R. K.

Foreign Animal Diseases. Their Prevention, Diagnosis and Control. Official Report of United States Livestock Sanitary Association, 1954. Pp. 265; 37 ills. Trenton: U. S. Livestock Sanitary Association, 1955. Price, $1.00.

THIS is an extremely valuable report on the important foreign animal diseases that might enter the United States and Canada either by accident or by deliberate acts of sabotage. Intended primarily for veterinarians, it should be of interest to public health officers and many physicians, since six of the twenty-five diseases discussed are transmissible to man. The subject matter is concise and well arranged with special attention to identification of the diseases, the symptoms, the pathological changes, the diagnosis, prognosis, epidemiology, control, and public health aspects. R. K.

Patho-Physiologie der Atmung in der Lungen-Chirurgie. By DR. MED. J. MAURATH, Tübingen. Pp. 80; 31 ills. Stuttgart: Georg Thieme Verlag, 1955 (Intercontinental Medical Book Corporation, New York, U. S. Agents). Price, $4.65.

A CONCISE and practical summary of the pathophysiology of respiration as studied in patients subjected to various operative procedures on the lungs. The first section is devoted to the description of tests used. Then follows the findings obtained by these methods in some normal controls and in a series of patients before these operative procedures and after an interval sufficiently long to evaluate the effect of the operation. Workers in this field who read German will find this a valuable contribution. R. K.

NEW EDITIONS

Klinische Elektrokardiographie. By DR. MAX HOLZMANN. 3rd ed. Pp. 688; 303 ills. Stuttgart: Georg Thieme Verlag, 1955 (Intercontinental Medical Book Corporation, New York, U. S. Agents). Price, $19.05.

THE previous edition has been very favorably reviewed in the past. The present edition has been brought up to the increased knowledge that has accumulated in the course of four years; this refers particularly to the chapters dealing with the abnormal Q–T duration, abnormal U waves, congenital cardiovascular anomalies and mitral stenosis, exercise tests, and evaluation of myocardial damage.

Vector-cardiography is considered in its theoretical and some practial aspects. Correlation with clinical data makes the presentation particularly valuable. The bibliography is extensive. The quality of print and reproduction is superior.

H. R.

Klinische Vorstellungen. By VIKTOR VON WEIZSÄCKER. 4th ed. Pp. 128. Stuttgart: Hippokrates Verlag, 1955. Price, DM 10.80.

"There is also a psychiatry without mind and an internal medicine without inner core." The author wants the center of gravity in medicine to shift from physico-chemical rationalism to an animistic-anthropological principle.

Apart from such declaration of creed, the book contains 30 excellently presented cases, mainly in the fields of organic-neurological and emotional disorders.

Readers sufficiently conversant with the German language will enjoy reading this book, which in Germany was almost a medical best-seller.

W. E.

Psychological Medicine. By DESMOND CURRAN, M.B., F.R.C.P., D.P.M., and MAURICE PARTRIDGE, M.A., D.M., D.P.M., Senior Consultant Psychiatrist and Consultant Psychiatrist, respectively, to St. George's Hospital. 4th ed. Pp. 407; 20 ills. Edinburgh and London: E. & S. Livingstone, Ltd., 1955 (Williams & Wilkins Co., Baltimore, U. S. Agents). Price, $5.00.

THIS is the fourth edition of a short introduction to psychiatry for students and practitioners. It is inclusive, however, and covers the field, the various entities, as well as discussing etiology, history taking, symptomatology and treatment. There is also a chapter on the legal aspects of mental illness. The approach is eclectic with, therefore, less emphasis upon psychodynamic formulations than has been current in this country recently. Moreover, the book does not have the revised classification and nomenclature adopted by the American Psychiatric Association in 1951 which would limit its usefulness for medical students. There are twenty illustrations, a bibliography and an index.

O. E.

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